PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07C 21/00, A01N 33/02 | A1

(11) International Publication Number: **WO 98/52890**

(43) International Publication Date: 26 November 1998 (26.11.98)

(21) International Application Number: PCT/US98/10264

(22) International Filing Date: 20 May 1998 (20.05.98)

(30) Priority Data:
60/047,338 21 May 1997 (21.05.97) US

(71) Applicant *(for all designated States except US)*: ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: FRITZ, James, Erwin [US/US]; 9757 North Moonstone Place, McCordsville, IN 46055 (US). HIPSKIND, Philip, Arthur [US/US]; 3660 South Farmstone Circle, New Palestine, IN 46163 (US). KALDOR, Stephen, Warren [US/US]; 7435 Burkwood Way, Indianapolis, IN 46254 (US). LOBB, Karen, Lynn [US/US]; 5625 East Lowell Avenue, Indianapolis, IN 46219 (US). NIXON, James, Arthur [US/US]; 7375 Taos Trail, Indianapolis, IN 46219 (US). SCOTT, William, Leonard [US/US]; 144 Buckingham Drive, Indianapolis, IN 46208 (US).

(74) Agents: GAYLO, Paul, J. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: 3–ARYLPROPYLAMINO NEUROPEPTIDE Y RECEPTOR ANTAGONISTS

(57) **Abstract**

This invention provides a series of substituted 3–arylpropylamines which are useful in treating or preventing a condition associated with an excess of neuropeptide Y. This invention also provides the substituted 3–arylpropylamines as well as pharmaceutical formulations which comprise as an active ingredient one or more of these substituted thiophenes.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

3-ARYLPROPYLAMINO NEUROPEPTIDE Y RECEPTOR ANTAGONISTS

This application claims the benefit of U.S. Provisional Patent Application Serial Number 60/047338 filed May 21, 1997.

Neuropeptide Y is a peptide present in the central and peripheral nervous systems. The peptide co-exists with noradrenaline in many neurons and acts as a neurotransmitter per se or synergistically together with noradrenaline. Neuropeptide Y-containing fibers are numerous around arteries in the heart, but are also found around the arteries in the respiratory tract, the gastrointestinal tract, and the genitourinary tract. Neuropeptide Y is also present in the cerebrum with effects on blood pressure, feeding, and the release of different hormones. Alterations in central concentrations of neuropeptide Y have been implicated in the etiology of psychiatric disorders.

Neuropeptide Y was discovered, isolated and sequenced in 1982 from porcine brain as part of a general screening protocol to discover carboxy-terminal amidated peptides and was named neuropeptide Y due to its isolation form neural tissue and the presence of tyrosine as both the amino and carboxy terminal amino acid. Neuropeptide Y is a member of the pancreatic family of peptides and shares significant sequence homology with pancreatic polypeptide, and peptide YY.

Neuropeptide Y and the other members of its family of peptides all feature a tertiary structure consisting of an N-terminal polyproline helix and an amphiphilic α-helix, connected with a β-turn, creating a hairpin-like loop, which is sometimes referred to as the pancreatic polypeptide (PP) fold. The helices are kept together by hydrophobic interactions. The amidated C-terminal end projects away from the hairpin loop.

Subsequent to its discovery neuropeptide Y was identified as being the most abundant peptide in the central nervous system with

widespread distribution including the cortex, brainstem, hippocampus, hypotahlamus, amygdala, and thalamus as well as being present in the peripheral nervous system in sympathetic neurons and adrenal chromaffin cells.

Neuropeptide Y seems to fulfill the main neurotransmitter criteria, as it is stored in synaptic granules, is released upon electrical nerve stimulation, and acts at specific receptors. It is clear that neuropeptide Y is an important messenger in its own right, probably in the brain, where neuropeptide Y potently inhibits the activity of adenylate cyclase and induces an increase in the intracellular levels of calcium. Central injection of neuropeptide Y results in blood pressure changes, increased feeding, increased fat storage, elevated blood sugar and insulin, decreased locomotor activity, reduced body temperature, and catalepsy.

Neuropeptide Y (as well as its chemical relatives) acts upon membrane receptors that are dependent on guanyl-nucleotide binding proteins, known as G protein-coupled receptors. G proteins are a family of membrane proteins that become activated only after binding guanosine triphosphate. Activated G proteins in turn activate an amplifier enzyme on the inner face of a membrane; the enzyme then converts precursor molecules into second messengers.

Neuropeptide Y appears to interact with a family of closely related receptors. These receptors are generally classified into several subtypes based upon the ability of different tissues and receptors to bind different fragments of neuropeptide Y and other members of the PP family of peptides. The Y1 receptor subtype appears to be the major vascular neuropeptide Y receptor. The Y2 receptor subtypes can also occur postjunctionally on vascular smooth muscle. The as-yet-unisolated Y3 receptor subtype appears to be neuropeptide Y-specific, not binding peptide YY. This receptor is likely to be present in the adrenal tissues, medulla, heart, and brain stem , among other areas. [For a review of neuropeptide Y

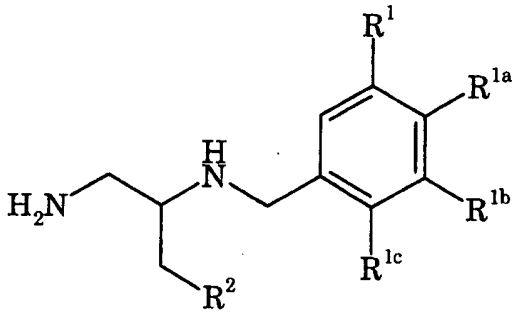
and neuropeptide Y receptors, see, e.g., C. Wahlestedt and D. Reis, Annual Review of Pharmacology and Toxicology, 33:309-352 (1993); D. Gehlert and P. Hipskind, Current Drug Design, in press].

In view of the wide number of clinical maladies associated with an excess of neuropeptide Y, the development of neuropeptide Y receptor antagonists will serve to control these clinical conditions. The earliest such receptor antagonists, such as Patent Cooperation Treaty Patent Publication WO 91/08223, published June 13, 1991, and Patent Cooperation Treaty Patent Publication WO 94/00486, published January 6, 1994, were peptide derivatives. These antagonists are of limited pharmaceutical utility because of their metabolic instability.

Patent Cooperation Treaty Patent Publication WO 97/09308, published March 13, 1997, describes a series of potent indolyl neuropeptide Y receptor antagonists. United States patent application 08/775,538, filed January 9, 1997 describe a series of potent benzimidazolyl neuropeptide Y receptor antagonists.

In essence, this invention provides a class of potent nonpeptidyl neuropeptide Y receptor antagonists. By virtue of their non-peptide nature, the compounds of the present invention do not suffer from the shortcomings, in terms of metabolic instability, of most known peptide-derived neuropeptide Y receptor antagonists.

This invention encompasses methods for the treatment or prevention of a physiological disorder associated with an excess of neuropeptide Y, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of Formula I



I

wherein:

R^1, R^{1a}, R^{1b}, and R^{1c} are independently hydrogen, halo, C_1-C_6 alkoxy, C_1-C_6 alkyl, trifluoromethyl, trifluoromethoxy, or phenyl;

or R^1 and R^{1a}, together with the benzo ring to which they are attached, form a 2-naphthyl group;

or R^{1b} and R^{1c}, together with the benzo ring to which they are attached, form a 1-naphthyl group;

provided that no more than one of R^1, R^{1a}, R^{1b}, and R^{1c} is phenyl;

R^2 is naphthyl, pyridyl, phenyl, benzothienyl, indanyl, indenyl, indolyl, benzofuryl, or pyrrolyl,

said phenyl being optionally substituted with one or more moieties selected from the group consisting of halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, and trifluoromethyl;

or a pharmaceutically acceptable salt or solvate thereof.

This invention also encompasses the novel compounds of Formula I as well as pharmaceutical formulations comprising a compound of Formula I in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients therefor.

The current invention concerns the discovery that a select group of substituted 3-arylpropylamines, those of Formula I, are useful as neuropeptide Y receptor antagonists. More specifically, these compounds are useful as antagonists of the neuropeptide Y5 receptor. United States Patent 5,602,024, issued February 11, 1997, describes methods for identifying compounds useful as antagonists of the human Y5 receptor.

"C_1-C_6 alkoxy" represents a straight or branched alkyl chain having from one to six carbon atoms attached to an oxygen atom. Typical C_1-C_6 alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, *t*-butoxy, pentoxy and the like. The term "C_1-C_6 alkoxy" includes within its definition the terms "C_1-C_4 alkoxy" and "C_1-C_3 alkoxy".

As used herein, the term "C_1-C_{12} alkyl" refers to straight or branched, monovalent, saturated aliphatic chains of 1 to 12 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, and hexyl. The term "C_1-C_{12} alkyl" includes within its definition the terms "C_1-C_6 alkyl" and "C_1-C_4 alkyl".

"Halo" represents chloro, fluoro, bromo or iodo.

The term "amino-protecting group" as used in the specification refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. Examples of such amino-protecting groups include formyl, trityl (herein abbreviated as "Tr"), phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, and urethane-type blocking groups such as benzyloxycarbonyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl,

4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, *t*-butoxycarbonyl (herein abbreviated as "BoC"), 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)-prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)-ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, fluorenylmethoxy-carbonyl ("FMOC"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl and the like; benzoylmethylsulfonyl group, 2-nitrophenylsulfenyl, diphenylphosphine oxide and like amino-protecting groups. The species of amino-protecting group employed is usually not critical so long as the derivatized amino group is stable to the condition of subsequent reactions on other positions of the intermediate molecule and can be selectively removed at the appropriate point without disrupting the remainder of the molecule including any other amino-protecting groups. Preferred amino-protecting groups are trityl, *t*-butoxycarbonyl (*t*-BOC), allyloxycarbonyl and benzyloxycarbonyl. Further examples of groups referred to by the above terms are described by E. Haslam, "Protective Groups in Organic Chemistry", (J.G.W. McOmie, ed., 1973), at Chapter 2; and T.W. Greene and P.G.M. Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, (1991), at Chapter 7.

The compounds of the present invention may have one or more asymmetric centers. As a consequence of these chiral centers, those compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All asymmetric forms, individual isomers and combinations thereof, are within the scope of the present invention.

The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" (*rectus*) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" (*sinister*) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in NOMENCLATURE OF ORGANIC COMPOUNDS: PRINCIPLES AND PRACTICE, (J.H. Fletcher, et al., eds., 1974) at pages 103-120.

In addition to the (R)-(S) system, the older D-L system may also be used in this document to denote absolute configuration, especially with reference to amino acids. In this system a Fischer projection formula is oriented so that the number 1 carbon of the main chain is at the top. The prefix "D" is used to represent the absolute configuration of the isomer in which the functional (determining) group is on the right side of the carbon atom at the chiral center and "L", that of the isomer in which it is on the left.

In order to preferentially prepare one optical isomer over its enantiomer, the skilled practitioner can proceed by one of two routes. The practitioner may first prepare the mixture of enantiomers and then separate the two enantiomers. A commonly employed method for the resolution of the racemic mixture (or mixture of enantiomers) into the individual enantiomers

is to first convert the enantiomers to diastereomers by way of forming a salt with an optically active salt or base. These diastereomers can then be separated using differential solubility, fractional crystallization, chromatography, or like methods. Further details regarding resolution of enantiomeric mixtures can be found in J. Jacques, et al., ENANTIOMERS, RACEMATES, AND RESOLUTIONS, (1991).

In addition to the schemes described above, the practitioner of this invention may also choose an enantiospecific protocol for the preparation of the compounds of Formula I. Such a protocol employs a synthetic reaction design which maintains the chiral center present in the starting material in a desired orientation. These reaction schemes usually produce compounds in which greater than 95 percent of the title product is the desired enantiomer.

As noted supra, this invention includes the pharmaceutically acceptable salts of the compounds defined by Formula I. A compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of organic and inorganic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic acid, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic

acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, γ-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, napththalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid and methanesulfonic acid.

Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen carries a suitable organic group such as an alkyl, alkenyl, alkynyl, or aralkyl moiety.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred.

It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

This invention further encompasses the pharmaceutically acceptable solvates of the compounds of Formulas I. Many of the Formula I compounds can combine with solvents such as water, methanol, ethanol and acetonitrile to form pharmaceutically acceptable solvates such as the corresponding hydrate, methanolate, ethanolate and acetonitrilate.

This invention also encompasses the pharmaceutically acceptable prodrugs of the compounds of Formula I. A prodrug is a drug which has been chemically modified and may be biologically inactive at its site of action, but which may be degraded or modified by one or more enzymatic or other in vivo processes to the parent bioactive form. This prodrug should have a different pharmacokinetic profile than the parent, enabling easier absorption across the mucosal epithelium, better salt formation or solubility, or improved systemic stability (an increase in plasma half-life, for example).

Typically, such chemical modifications include:

1) ester or amide derivatives which may be cleaved by esterases or lipases;

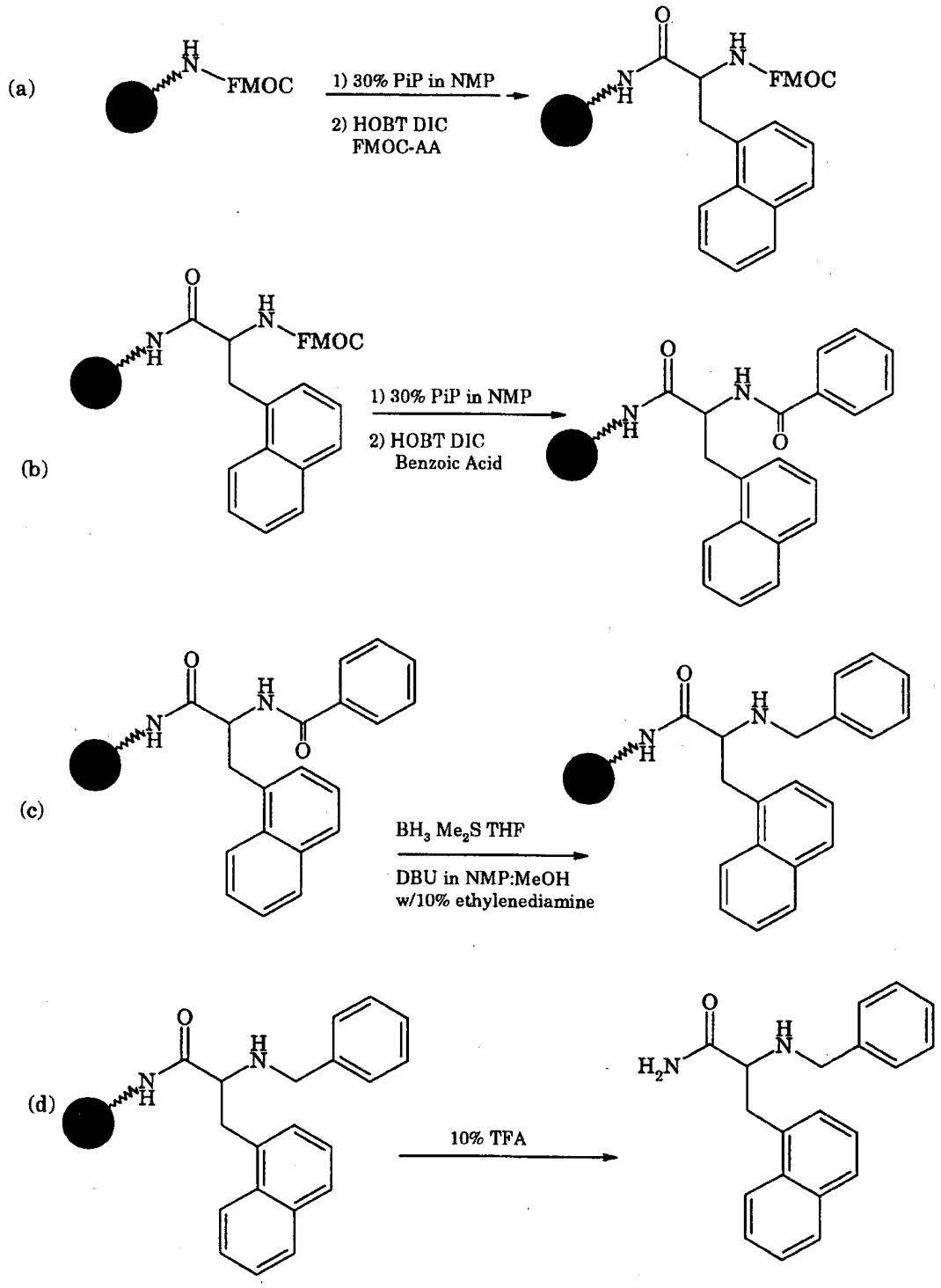
2) peptides which may be recognized by specific or nonspecific proteases; or

3) derivatives that accumulate at a site of action through membrane selection of a prodrug form or a modified prodrug form; or any combination of 1 to 3, supra. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in H, Bundgaard, DESIGN OF PRODRUGS, (1985).

The compounds of the present invention are generally prepared using several methods known to those of ordinary skill in the art. A most preferred means of synthesizing the compounds of Formula I employs combinatorial chemistry efforts utilizing commercially available reagents. One such effort is depicted in Scheme I, infra.

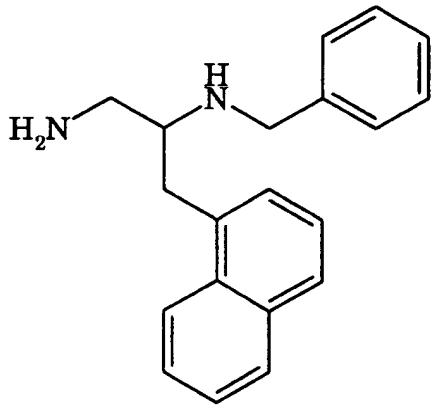
Generally, in such an effort, a portion of the molecule is covalently linked to a support. Such a support may be a resin bead, the wall of a container, some type of removable fiber or post, or any similar support. Such a bound molecule may then serve as a lattice or scaffold upon which the remainder of the molecule is formed. The covalent linkage to the support provides for rapid, quantitative purification of the molecule of interest. After the series of reactions has been performed, the molecule is cleaved from the support using standard chemistry means. One such way of removing the molecule of interest from the support is depicted below.

Scheme I


(a)
FMOC
1) 30% PiP in NMP
2) HOBT DIC
FMOC-AA
(b)
FMOC
1) 30% PiP in NMP
2) HOBT DIC
Benzoic Acid
(c)
BH3 Me2S THF
DBU in NMP:MeOH
w/10% ethylenediamine
(d)
10% TFA
H2N

Example 1

Preparation of 2-benzylamino-3-(naphth-1-yl)propylamine



Rink amide resin (3.0 g, 1.41 mmol) (Novabiochem, loading capacity 0.47 mmol/g) was slurried in 30% piperidine in N-methylpyrrolidone (40 ml total). After thirty minutes the resin was filtered and the reaction repeated, after which the resin was washed with N-methylpyrrolidone (4 x 80 ml). To the deprotected resin in 40 ml of N-methylpyrrolidone were added FMOC-D,L-3-(naphth-1-yl)alanine (1.85 g, 4.2 mmol), hydroxybenztriazole (0.57 g, 4.2 mmol), and 1,3-diisopropylcarbodiimide(0.53 g, 4.2 mmol). The resulting mixture was shaken for about 18 hours. After the reaction was filtered, and the coupling repeated, the reaction was washed with N-methylpyrrolidone (4 x 40 ml) and methylene chloride (2 x 40 ml) to afford the amino-protected 3-(naphth-1-yl)alanine coupled to the rink resin.

The amino-protected 3-(naphth-1-yl)alanine coupled to the rink resin was deprotected by slurrying in 45 ml of 30% piperidine in N-methylpyrrolidone for thirty minutes and was then filtered. The reaction mixture was repeated and the resin was washed in N-methylpyrrolidone (3 x 40 ml) and methylene chloride (3 x 40 ml). The resin was dried under

vacuum and split into 20 separate 150 mg portions and loaded into glass reaction vials.

To the deprotected amino acid resin (150 mg, 0.07 mmol) in 2 ml of N-methylpyrrolidone were added hydroxybenztriazole (28 mg, 0.21 mmol), and 1,3-diisopropylcarbodiimide(26 mg, 0.21 mmol) and benzoic acid (25.6 mg, 0.21 mmol). After four hours the reaction mixture was filtered and the coupling was repeated for 18 hours using fresh reagents. The reaction mixtures were filtered and washed with N-methylpyrrolidone (3 x 2 ml) and tetrahydrofuran (3 x 2 ml) to afford an N-acyl amino acid linked to the resin.

The carboxamide resulting from above (150 mg, 0.07 mmol) was reduced to the corresponding amine by slurrying in borane dimethyl sulfide complex (2 ml of a 1.25 M solution in tetrahydrofuran) and shaken for 18-36 hours. When complete, the reactions were filtered and washed with 0.06 M 1,8-diazabicyclo[5.4.0]undec-7-ene in 9:1 N-methylpyrrolidone in methanol with 10% ethylene diamine and shaken for at least six hours. The reacitons were filtered and the purification repeated for at least six more hours. The reaction mixtures were then filtered and washed with methylene chloride (3 x 2 ml), methanol (2 x 2 ml), methylene chloride (2 x 2 ml), methanol (1 x 2 ml) and methylene chloride (3 x 2 ml) to afford a reduced amino acid linked to the resin.

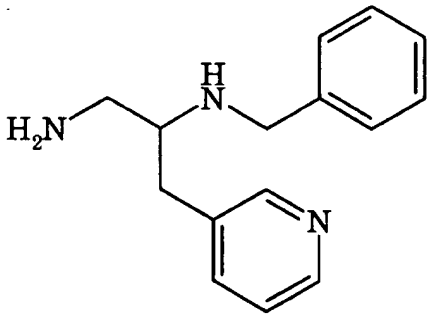
The amino acid was cleaved from the resin by treating wtih 10% trifluoroacetic acid in methylene chloride for 45 minutes and the resin filtered and washed with 3 ml methylene chloride. The filtrate was collected and concentrated. The resulting residues were loaded onto SCX columns (VARIAN® SCX column 3 x 500 mg) and washed with methanol (3 x 3 ml). The products were eulted off the column suing 2 M ammonia in methanol and concentrated to afford clear oils. Yield: 56%.

MS 291

The following compounds are prepared essentially as described above, employing analogous aryl carboxylic acids in place of the benzoic acid employed supra.

Example 2

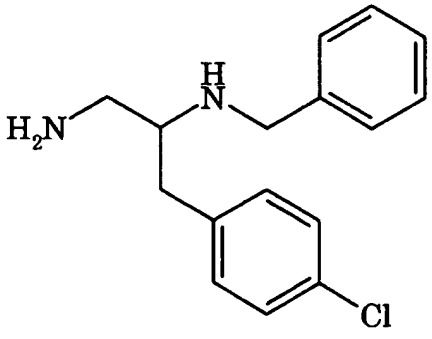
Preparation of 2-benzylamino-3-(pyridin-3-yl)propylamine



MS 242

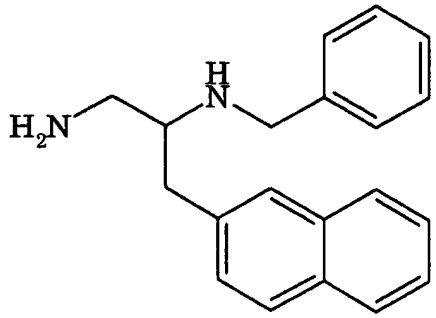
Example 3

Preparation of 2-benzylamino-3-(4-chlorophenyl)propylamine



Example 4

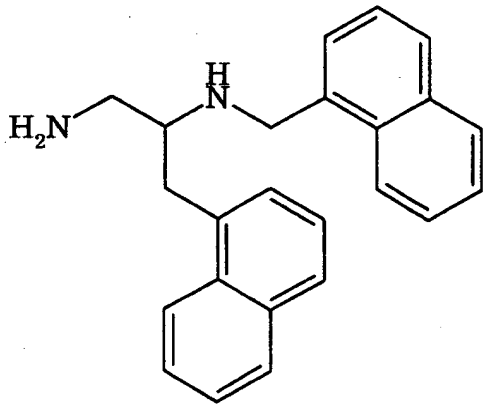
Preparation of 2-benzylamino-3-(naphth-2-yl)propylamine



MS 291

Example 5

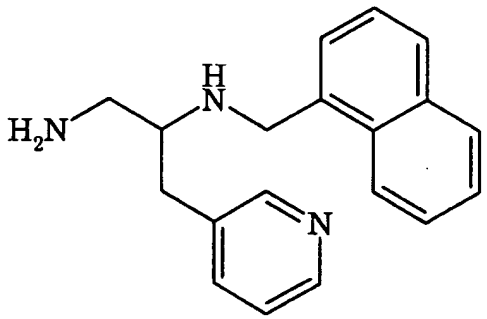
Preparation of 2-[(naphth-1-yl)methylamino]-3-(naphth-1-yl)propylamine



MS 341

Example 6

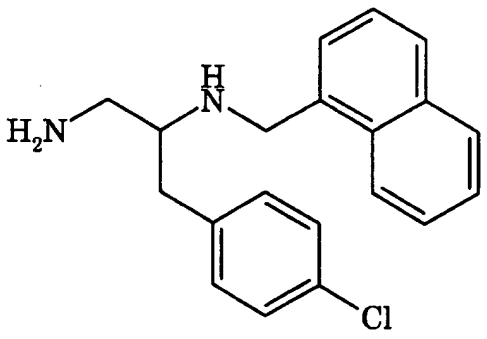
Preparation of 2-[(naphth-1-yl)methylamino]-3-(pyridin-3-yl)propylamine



MS 292

Example 7

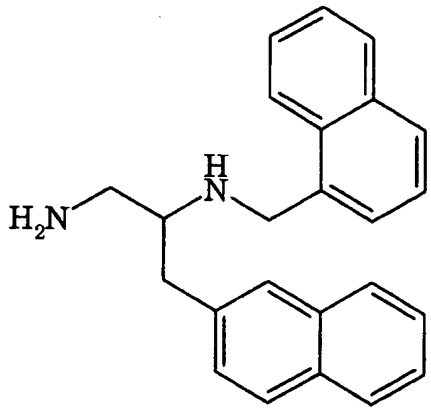
Preparation of 2-[(naphth-1-yl)methylamino]-3-(4-chlorophenyl)propylamine



MS 326

Example 8

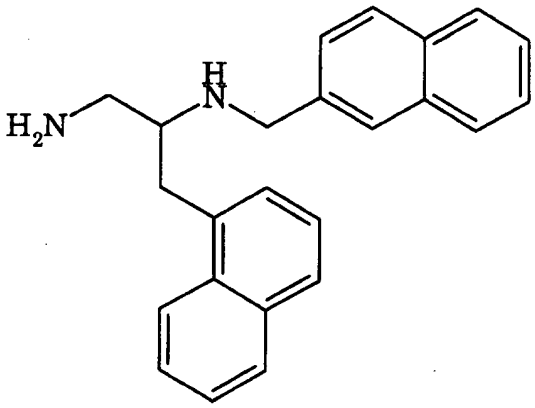
Preparation of 2-[(naphth-1-yl)methylamino]-3-(naphth-2-yl)propylamine



MS 341

Example 9

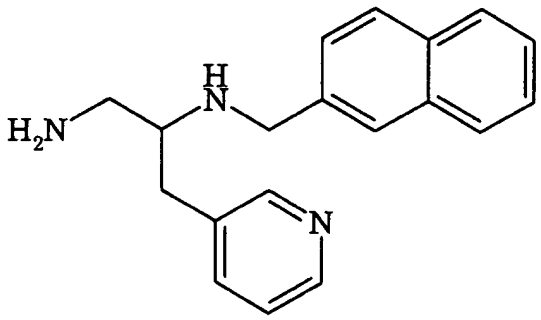
Preparation of 2-[(naphth-2-yl)methylamino]-3-(naphth-1-yl)propylamine



MS 341

Example 10

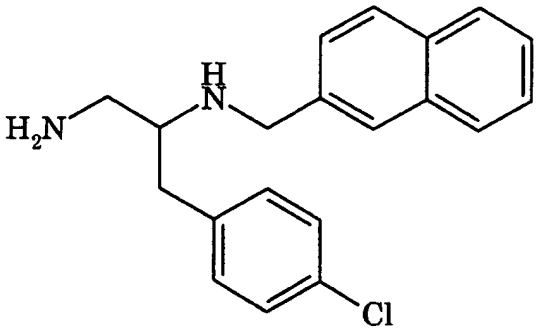
Preparation of 2-[(naphth-2-yl)methylamino]-3-(pyridin-3-yl)propylamine



MS 292

Example 11

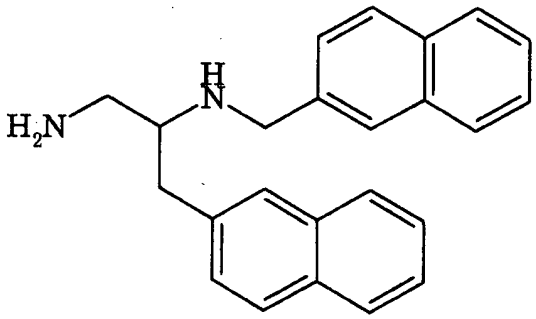
Preparation of 2-[(naphth-2-yl)methylamino]-3-(4-chlorophenyl)propylamine



MS 326

Example 12

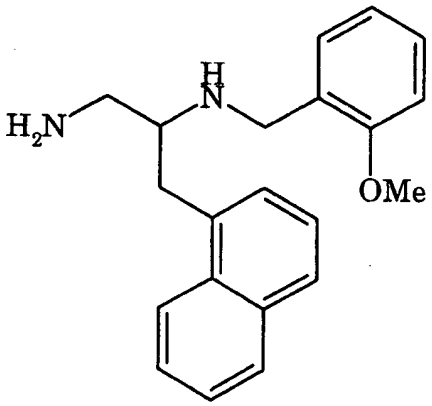
Preparation of 2-[(naphth-2-yl)methylamino]-3-(naphth-2-yl)propylamine



MS 341

Example 13

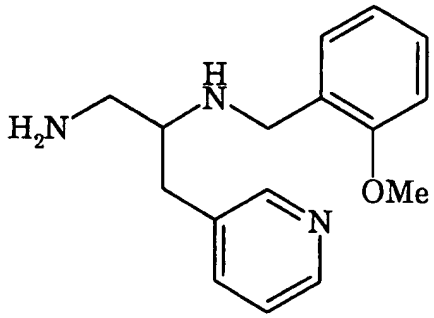
Preparation of 2-(2-methoxybenzylamino)-3-(naphth-1-yl)propylamine



MS 321

Example 14

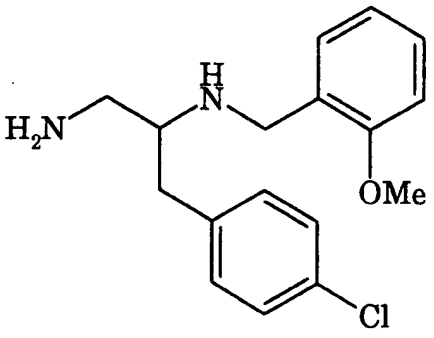
Preparation of 2-(2-methoxybenzylamino)-3-(pyridin-3-yl)propylamine



MS 272

Example 15

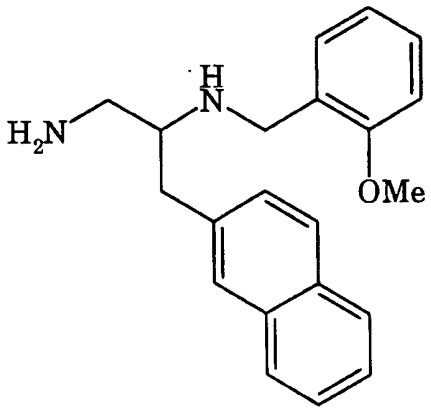
Preparation of 2-(2-methoxybenzylamino)-3-(4-chlorophenyl)propylamine



MS 305

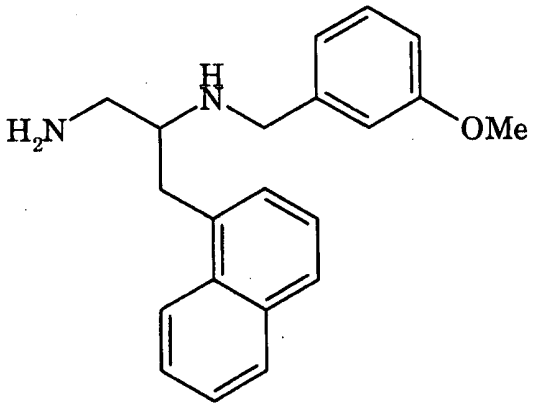
Example 16

Preparation of 2-(2-methoxybenzylamino)-3-(naphth-2-yl)propylamine



Example 17

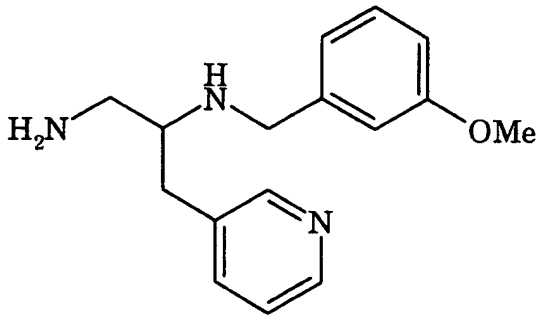
Preparation of 2-(3-methoxybenzylamino)-3-(naphth-1-yl)propylamine



MS 321

Example 18

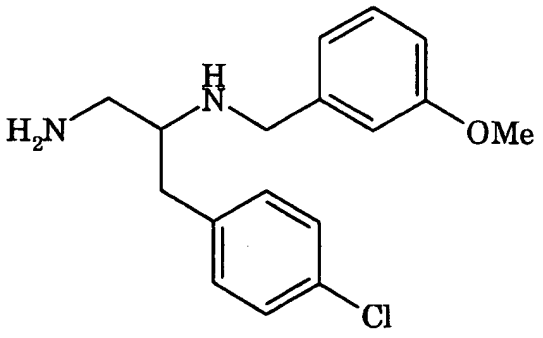
Preparation of 2-(3-methoxybenzylamino)-3-(pyridin-3-yl)propylamine



MS 272

Example 19

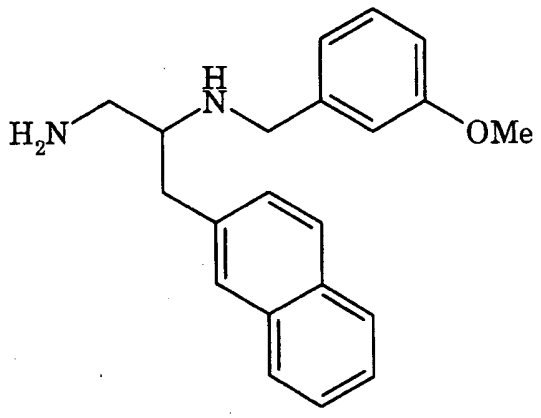
Preparation of 2-(3-methoxybenzylamino)-3-(4-chlorophenyl)propylamine



MS 305

Example 20

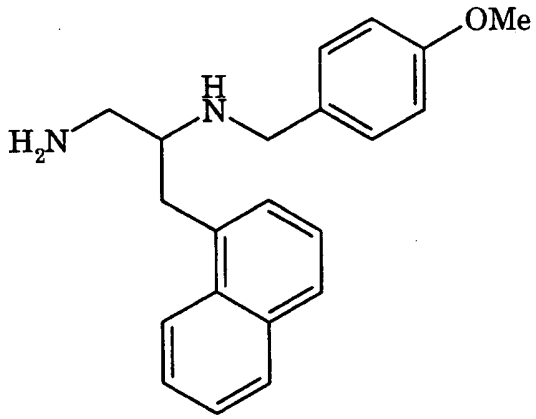
Preparation of 2-(3-methoxybenzylamino)-3-(naphth-2-yl)propylamine



MS 321

Example 21

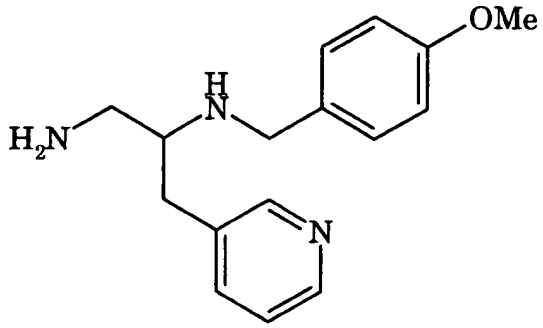
Preparation of 2-(4-methoxybenzylamino)-3-(naphth-1-yl)propylamine



MS 321

Example 22

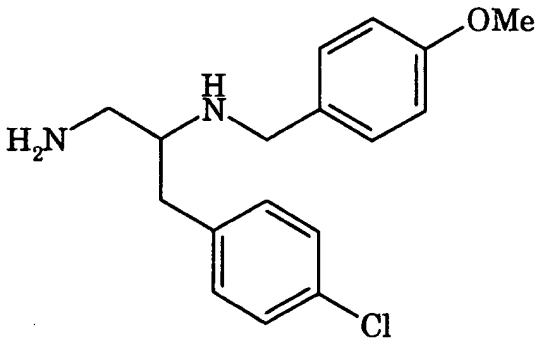
Preparation of 2-(4-methoxybenzylamino)-3-(pyridin-3-yl)propylamine



MS 272

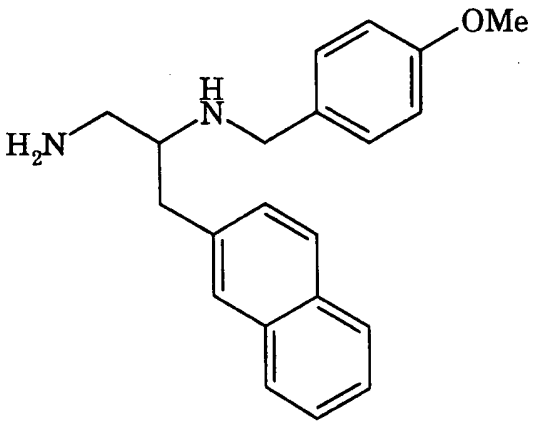
Example 23

Preparation of 2-(4-methoxybenzylamino)-3-(4-chlorophenyl)propylamine



Example 24

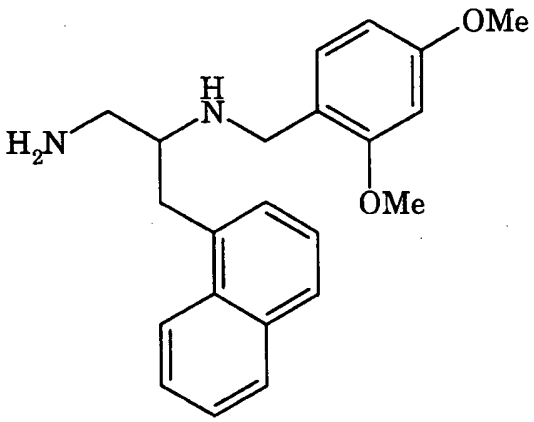
Preparation of 2-(4-methoxybenzylamino)-3-(naphth-2-yl)propylamine



MS 321

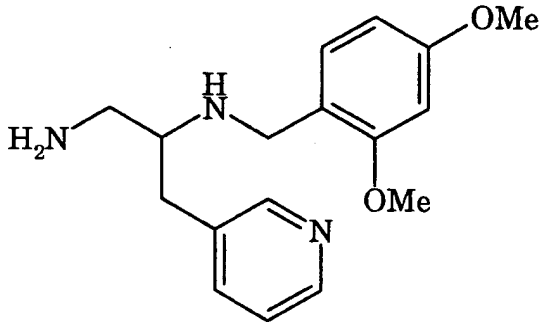
Example 25

Preparation of 2-(2,4-dimethoxybenzylamino)-3-(naphth-1-yl)propylamine



Example 26

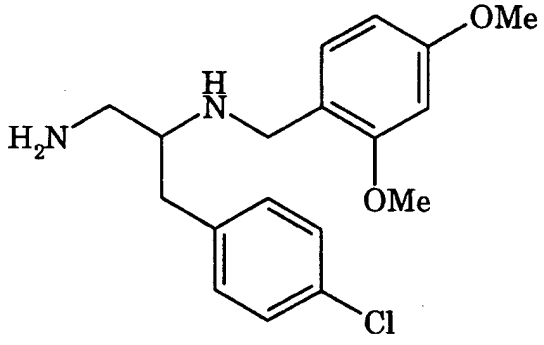
Preparation of 2-(2,4-dimethoxybenzylamino)-3-(pyridin-3-yl)propylamine



MS 302

Example 27

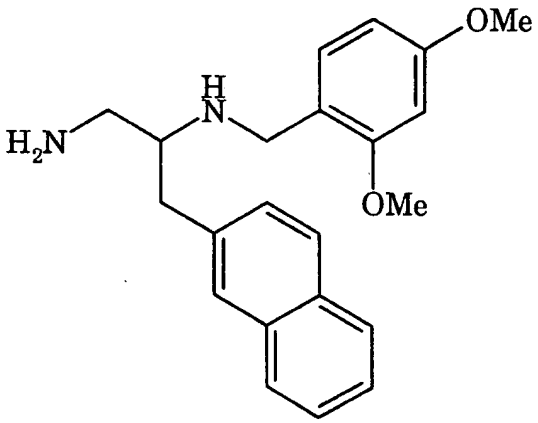
Preparation of 2-(2,4-dimethoxybenzylamino)-3-(4-chlorophenyl)propylamine



MS 336

Example 28

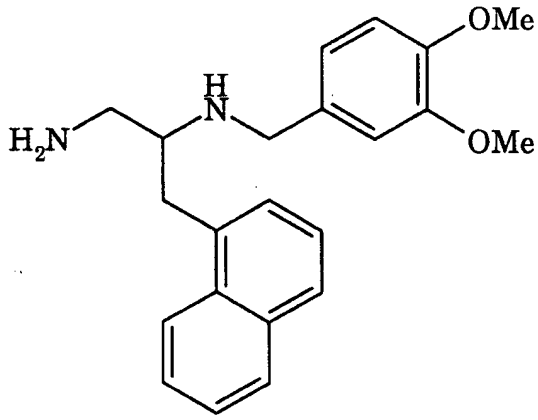
Preparation of 2-(2,4-dimethoxybenzylamino)-3-(naphth-2-yl)propylamine



MS 351

Example 29

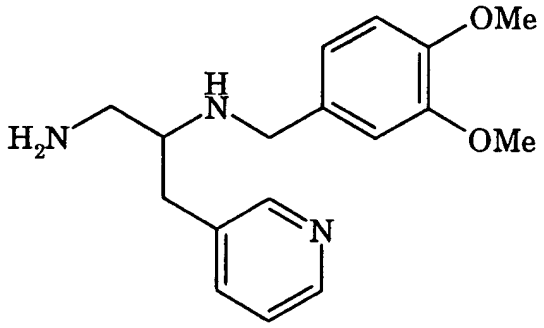
Preparation of 2-(3,4-dimethoxybenzylamino)-3-(naphth-1-yl)propylamine



MS 351

Example 30

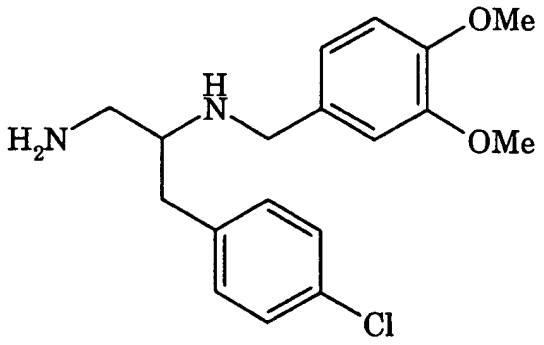
Preparation of 2-(3,4-dimethoxybenzylamino)-3-(pyridin-3-yl)propylamine



MS 302

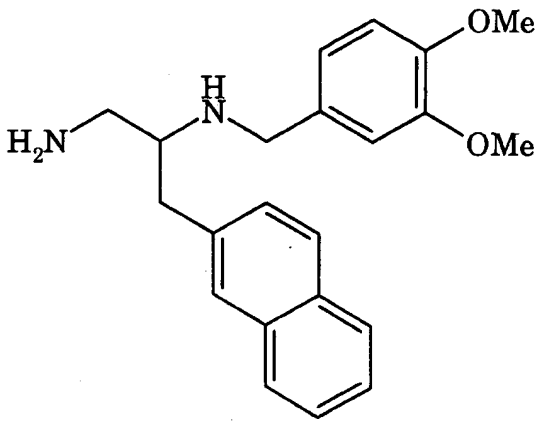
Example 31

Preparation of 2-(3,4-dimethoxybenzylamino)-3-(4-chlorophenyl)propylamine



Example 32

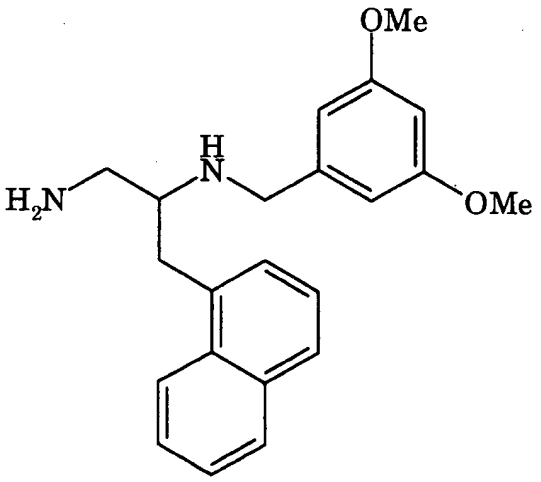
Preparation of 2-(3,4-dimethoxybenzylamino)-3-(naphth-2-yl)propylamine



MS 351

Example 33

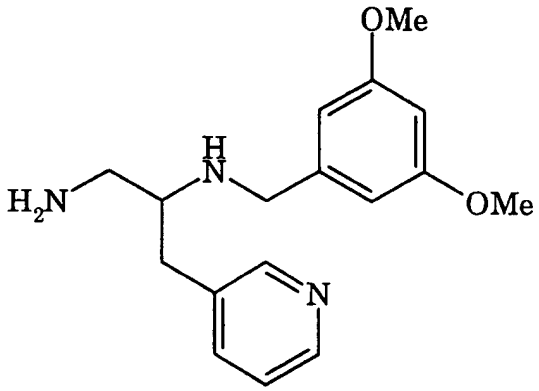
Preparation of 2-(3,5-dimethoxybenzylamino)-3-(naphth-1-yl)propylamine



MS 351

Example 34

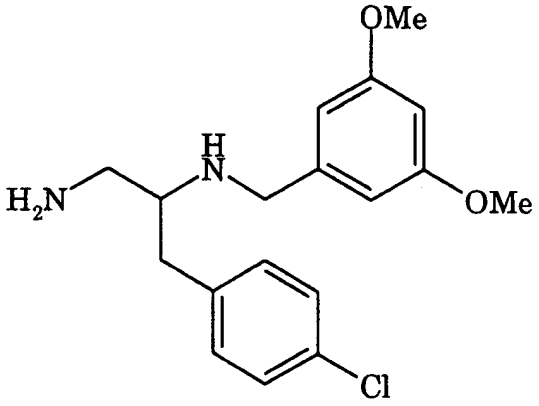
Preparation of 2-(3,5-dimethoxybenzylamino)-3-(pyridin-3-yl)propylamine



MS 302

Example 35

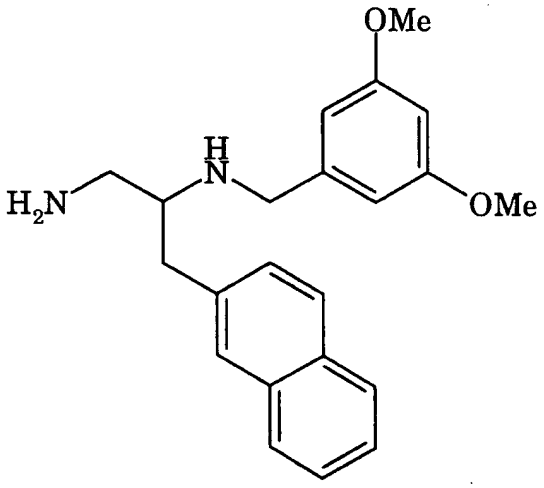
Preparation of 2-(3,5-dimethoxybenzylamino)-3-(4-chlorophenyl)propylamine



MS 336

Example 36

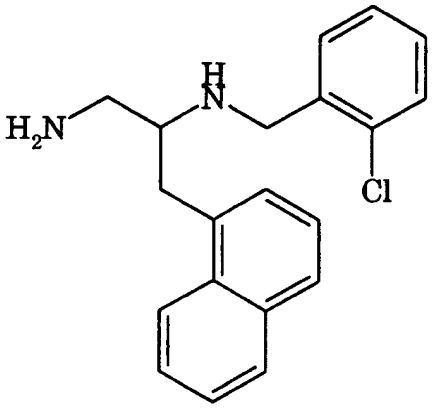
Preparation of 2-(3,5-dimethoxybenzylamino)-3-(naphth-2-yl)propylamine



MS 351

Example 37

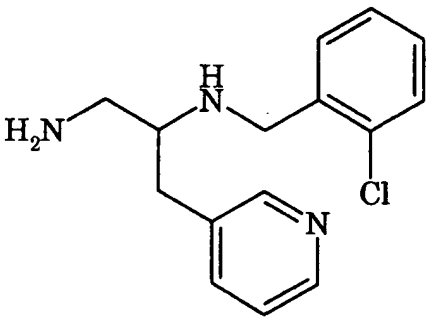
Preparation of 2-(2-chlorobenzylamino)-3-(naphth-1-yl)propylamine



MS 325

Example 38

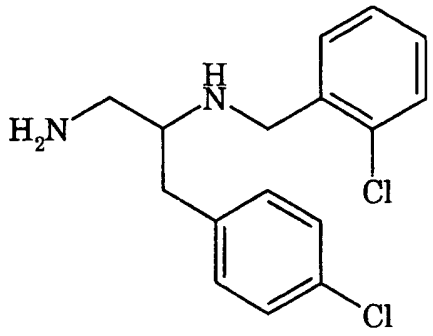
Preparation of 2-(2-chlorobenzylamino)-3-(pyridin-3-yl)propylamine



MS 276

Example 39

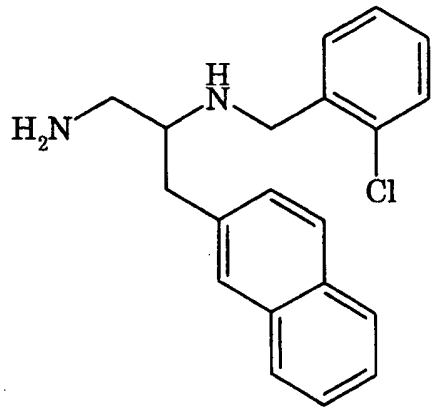
Preparation of 2-(2-chlorobenzylamino)-3-(4-chlorophenyl)propylamine



MS 311

Example 40

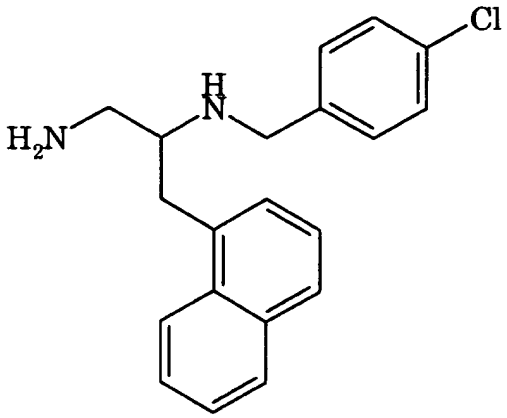
Preparation of 2-(2-chlorobenzylamino)-3-(naphth-2-yl)propylamine



MS 325

Example 41

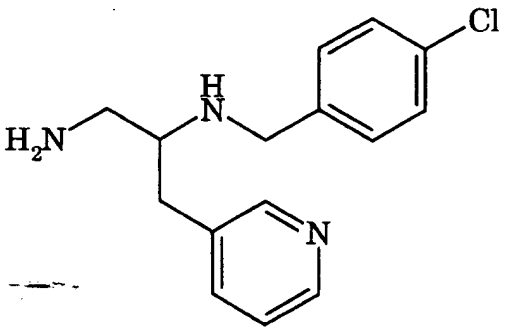
Preparation of 2-(4-chlorobenzylamino)-3-(naphth-1-yl)propylamine



MS 325

Example 42

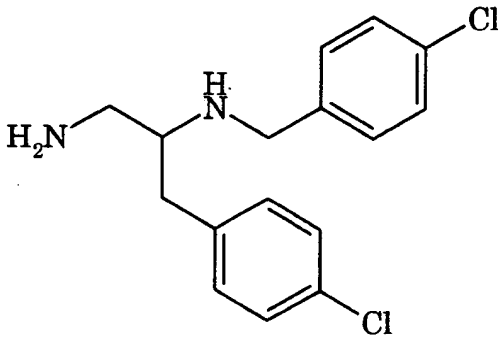
Preparation of 2-(4-chlorobenzylamino)-3-(pyridin-3-yl)propylamine



MS 276

Example 43

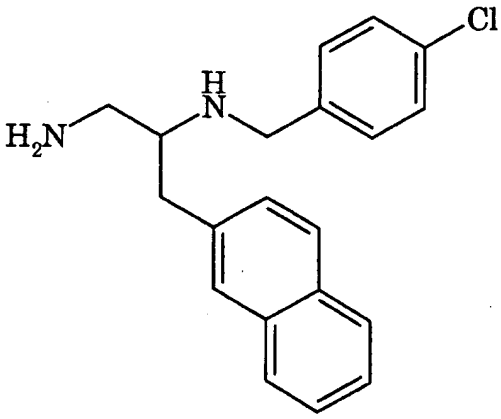
Preparation of 2-(4-chlorobenzylamino)-3-(4-chlorophenyl)propylamine



MS 311

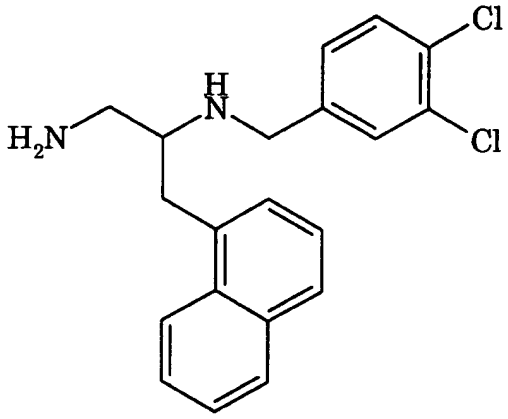
Example 44

Preparation of 2-(4-chlorobenzylamino)-3-(naphth-2-yl)propylamine



Example 45

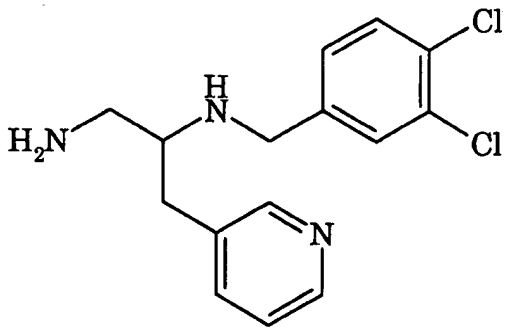
Preparation of 2-(3,4-dichlorobenzylamino)-3-(naphth-1-yl)propylamine



MS 359

Example 46

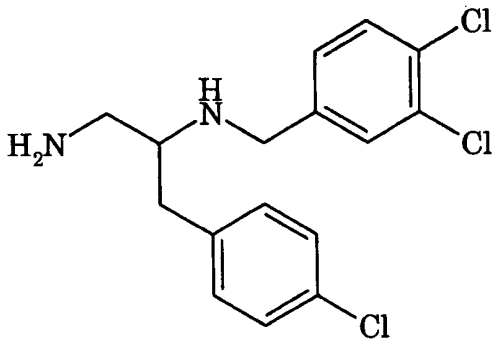
Preparation of 2-(3,4-dichlorobenzylamino)-3-(pyridin-3-yl)propylamine



MS 310

Example 47

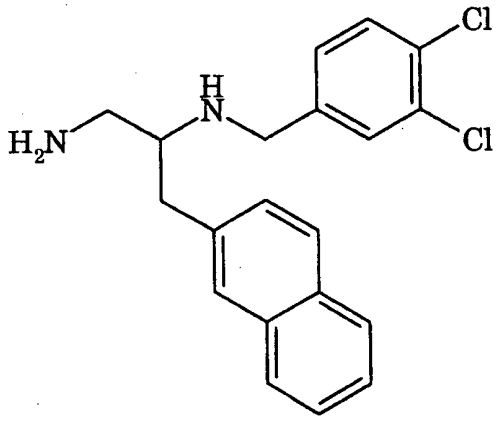
Preparation of 2-(3,4-dichlorobenzylamino)-3-(4-chlorophenyl)propylamine



MS 345

Example 48

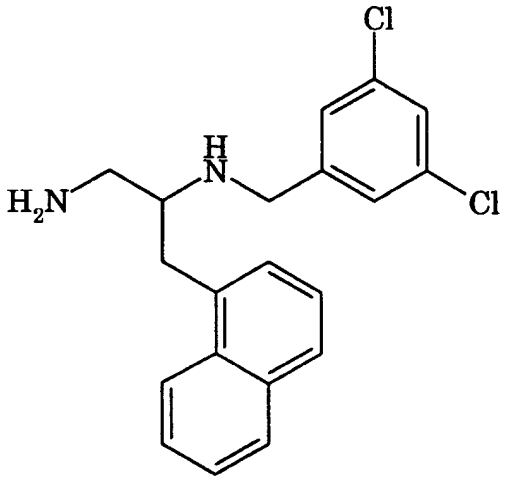
Preparation of 2-(3,4-dichlorobenzylamino)-3-(naphth-2-yl)propylamine



MS 359

Example 49

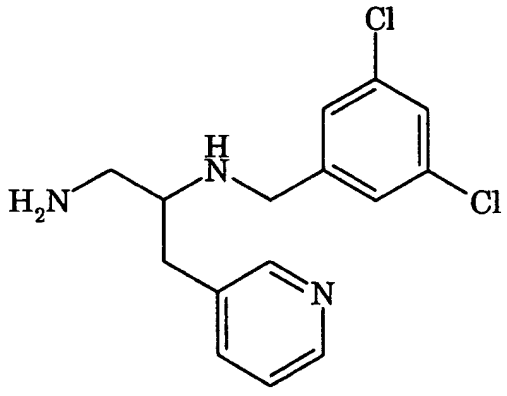
Preparation of 2-(3,5-dichlorobenzylamino)-3-(naphth-1-yl)propylamine



MS 359

Example 50

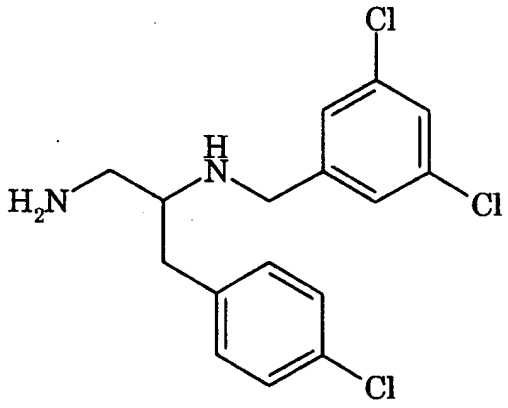
Preparation of 2-(3,5-dichlorobenzylamino)-3-(pyridin-3-yl)propylamine



MS 310

Example 51

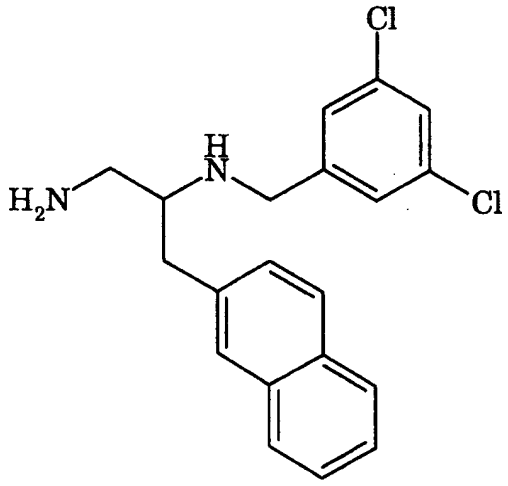
Preparation of 2-(3,5-dichlorobenzylamino)-3-(4-chlorophenyl)propylamine



MS 345

Example 52

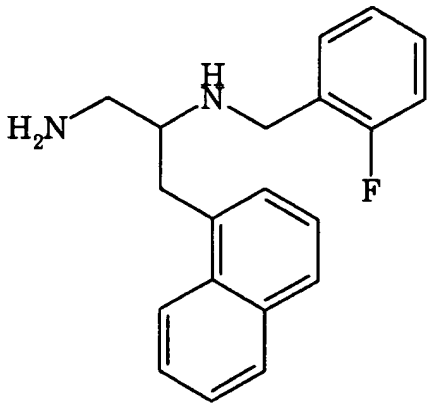
Preparation of 2-(3,5-dichlorobenzylamino)-3-(naphth-2-yl)propylamine



MS 359

Example 53

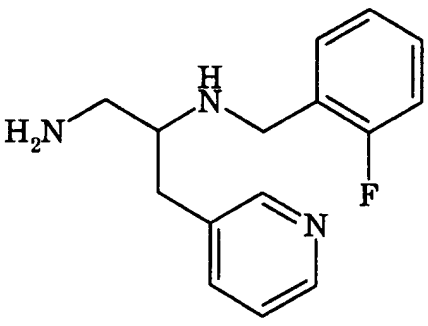
Preparation of 2-(2-fluorobenzylamino)-3-(naphth-1-yl)propylamine



MS 309

Example 54

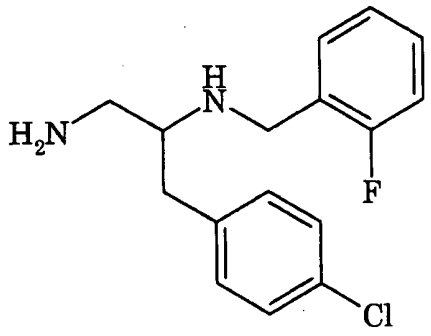
Preparation of 2-(2-fluorobenzylamino)-3-(pyridin-3-yl)propylamine



MS 260

Example 55

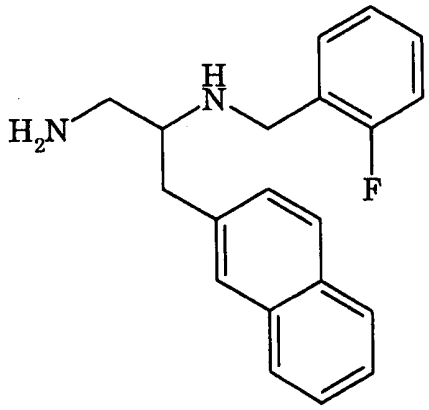
Preparation of 2-(2-fluorobenzylamino)-3-(4-chlorophenyl)propylamine



MS 294

Example 56

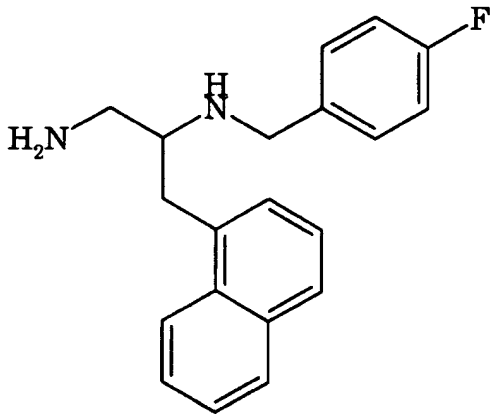
Preparation of 2-(2-fluorobenzylamino)-3-(naphth-2-yl)propylamine



MS 309

Example 57

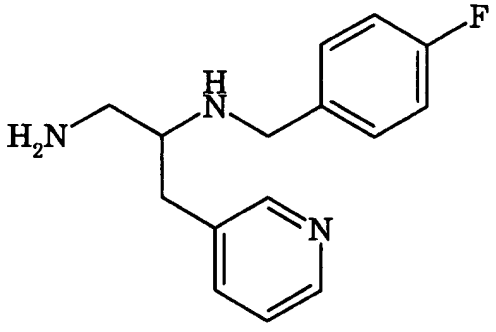
Preparation of 2-(4-fluorobenzylamino)-3-(naphth-1-yl)propylamine



MS 309

Example 58

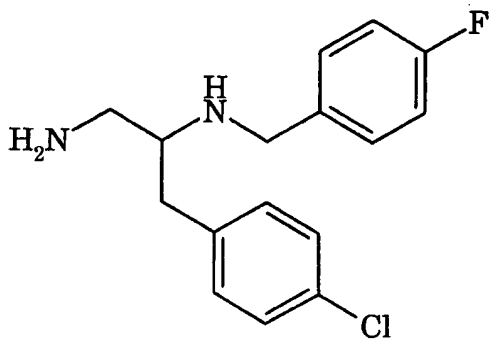
Preparation of 2-(4-fluorobenzylamino)-3-(pyridin-3-yl)propylamine



MS 260

Example 59

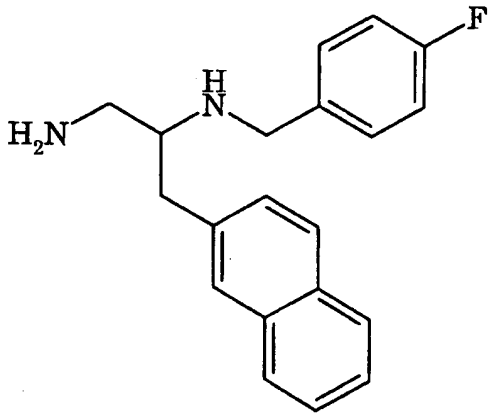
Preparation of 2-(4-fluorobenzylamino)-3-(4-chlorophenyl)propylamine



MS 294

Example 60

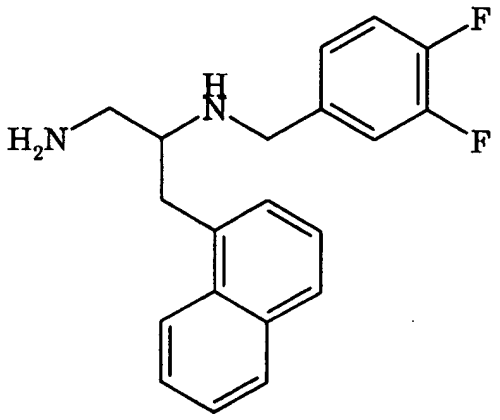
Preparation of 2-(4-fluorobenzylamino)-3-(naphth-2-yl)propylamine



MS 309

Example 61

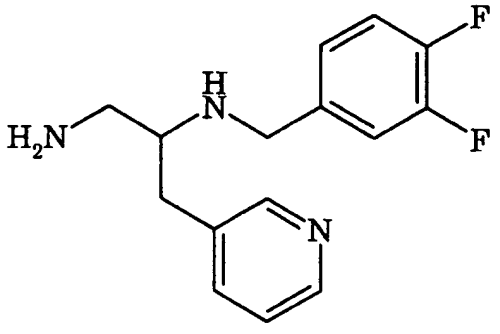
Preparation of 2-(3,4-difluorobenzylamino)-3-(naphth-1-yl)propylamine



MS 327

Example 62

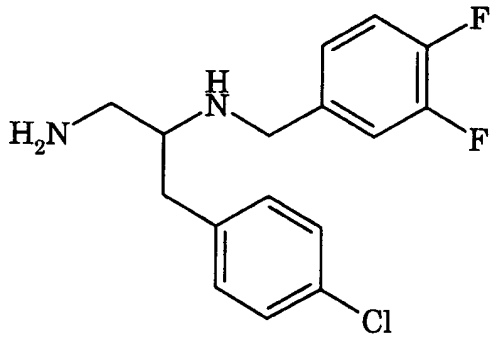
Preparation of 2-(3,4-difluorobenzylamino)-3-(pyridin-3-yl)propylamine



MS 278

Example 63

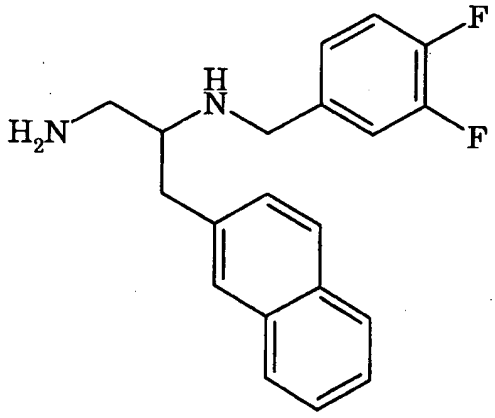
Preparation of 2-(3,4-difluorobenzylamino)-3-(4-chlorophenyl)propylamine



MS 312

Example 64

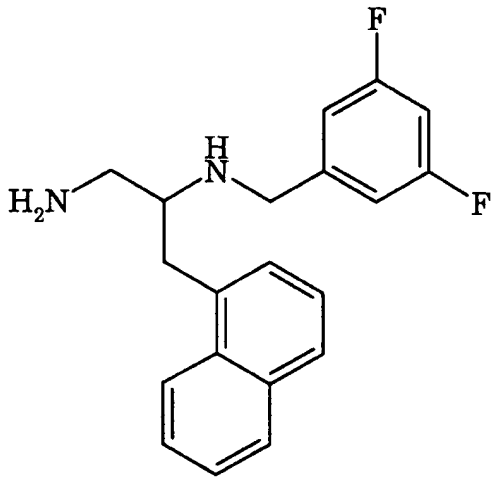
Preparation of 2-(3,4-difluorobenzylamino)-3-(naphth-2-yl)propylamine



MS 327

Example 65

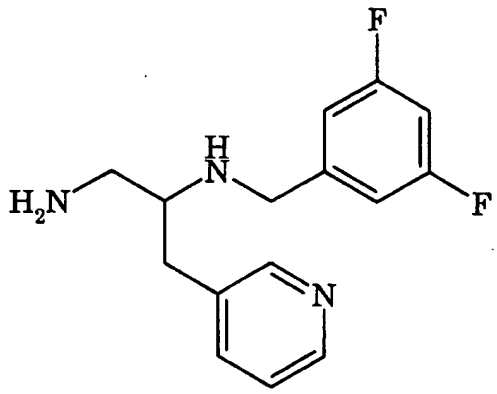
Preparation of 2-(3,5-difluorobenzylamino)-3-(naphth-1-yl)propylamine



MS 327

Example 66

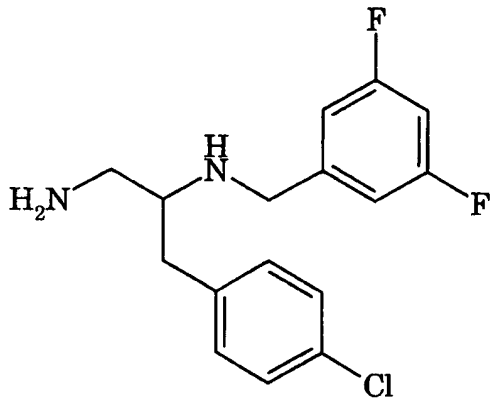
Preparation of 2-(3,5-difluorobenzylamino)-3-(pyridin-3-yl)propylamine



MS 278

Example 67

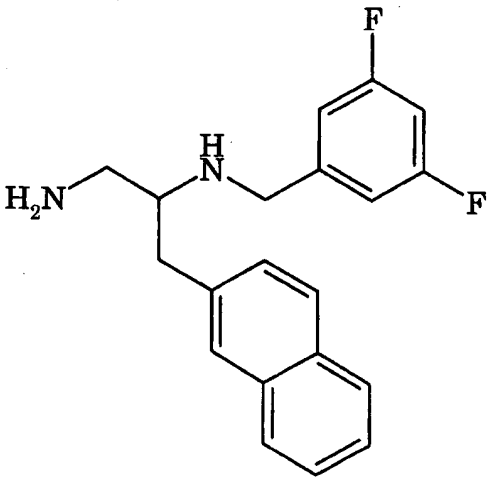
Preparation of 2-(3,5-difluorobenzylamino)-3-(4-chlorophenyl)propylamine



MS 312

Example 68

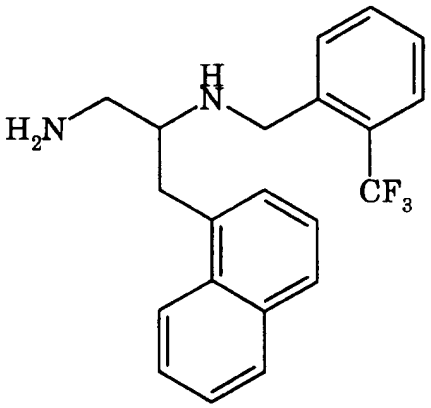
Preparation of 2-(3,5-difluorobenzylamino)-3-(naphth-2-yl)propylamine



MS 327

Example 69

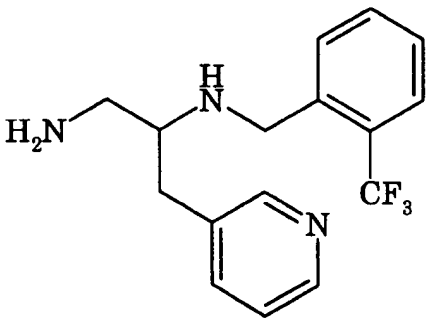
Preparation of 2-(2-trifluoromethylbenzylamino)-3-(naphth-1-yl)propylamine



MS 359

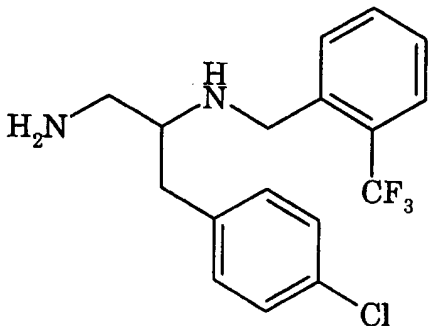
Example 70

Preparation of 2-(2-trifluoromethylbenzylamino)-3-(pyridin-3-yl)propylamine



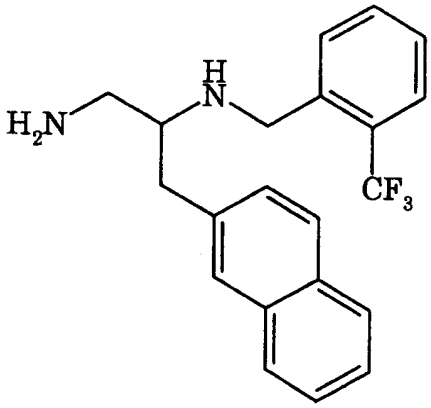
Example 71

Preparation of 2-(2-trifluoromethylbenzylamino)-3-(4-chlorophenyl)propylamine



Example 72

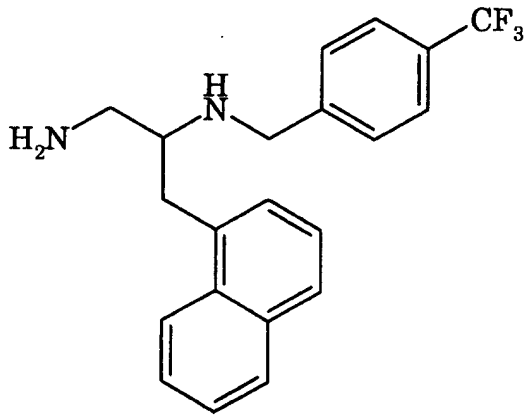
Preparation of 2-(2-trifluoromethylbenzylamino)-3-(naphth-2-yl)propylamine



MS 359

Example 73

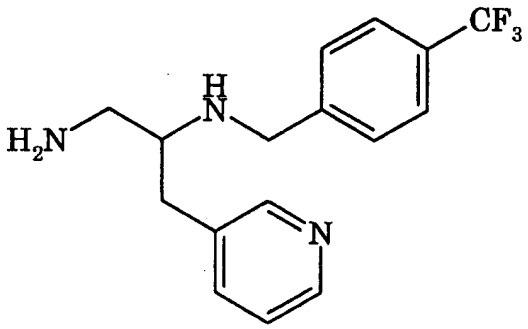
Preparation of 2-(4-trifluoromethylbenzylamino)-3-(naphth-1-yl)propylamine



MS 359

Example 74

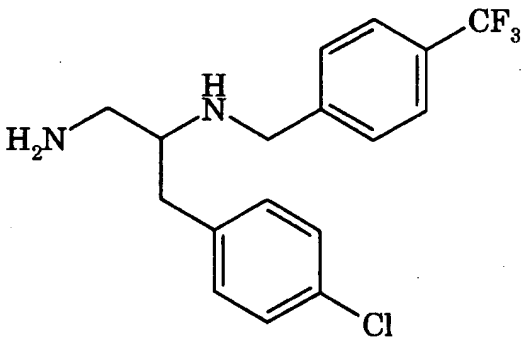
Preparation of 2-(4-trifluoromethylbenzylamino)-3-(pyridin-3-yl)propylamine



MS 310

Example 75

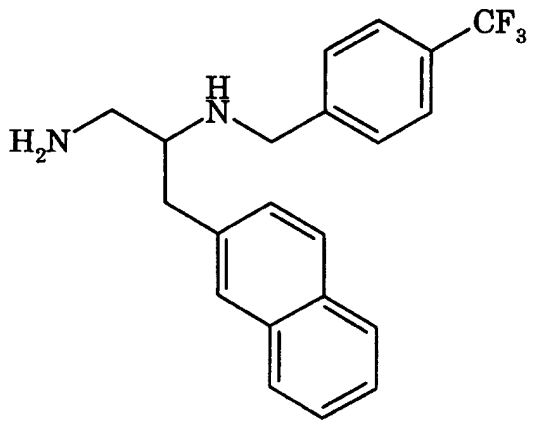
Preparation of 2-(4-trifluoromethylbenzylamino)-3-(4-chlorophenyl)propylamine



MS 344

Example 76

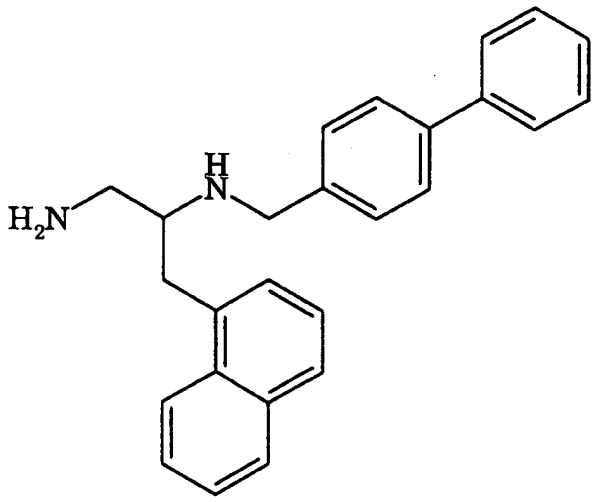
Preparation of 2-(4-trifluoromethylbenzylamino)-3-(naphth-2-yl)propylamine



MS 359

Example 77

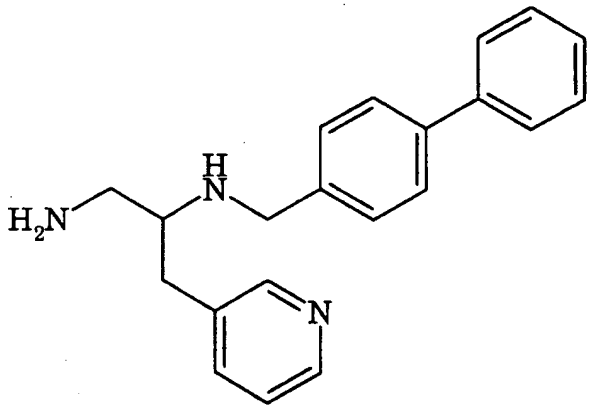
Preparation of 2-(4-phenylbenzylamino)-3-(naphth-1-yl)propylamine



MS 367

Example 78

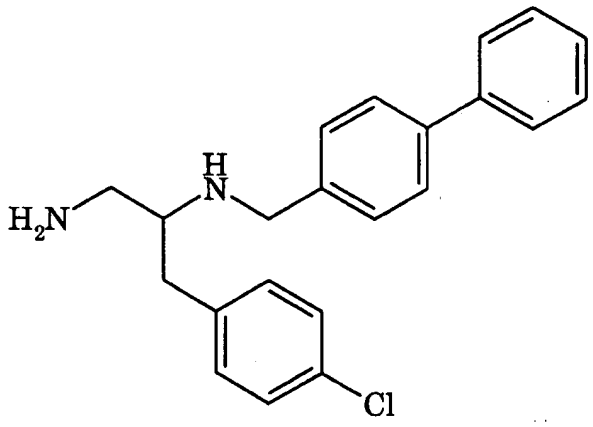
Preparation of 2-(4-phenylbenzylamino)-3-(pyridin-3-yl)propylamine



MS 318

Example 79

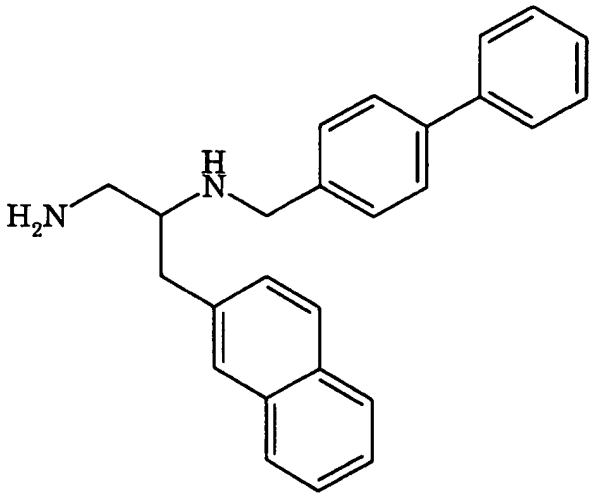
Preparation of 2-(4-phenylbenzylamino)-3-(4-chlorophenyl)propylamine



MS 352

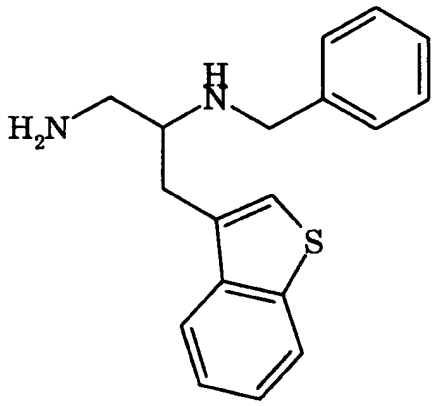
Example 80

Preparation of 2-(4-phenylbenzylamino)-3-(naphth-2-yl)propylamine



Example 81

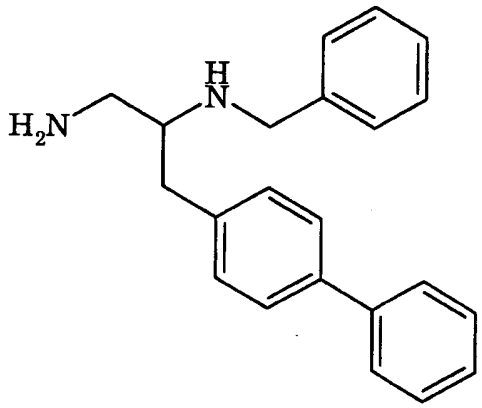
Preparation of 2-[(phenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 297

Example 82

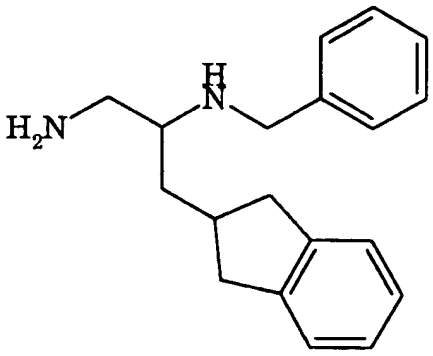
Preparation of 2-[benzylamino]-3-(4-biphenyl)propylamine



MS 317

Example 83

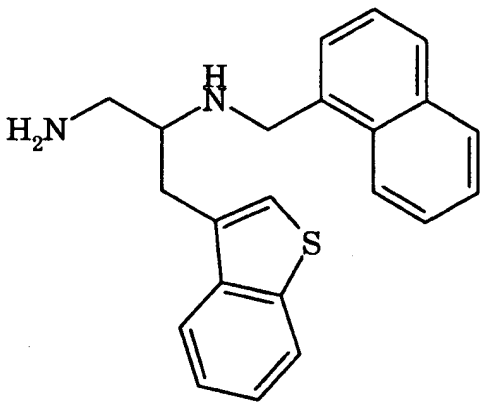
Preparation of 2-[benzylamino]-3-(indan-2-yl)propylamine



MS 341

Example 84

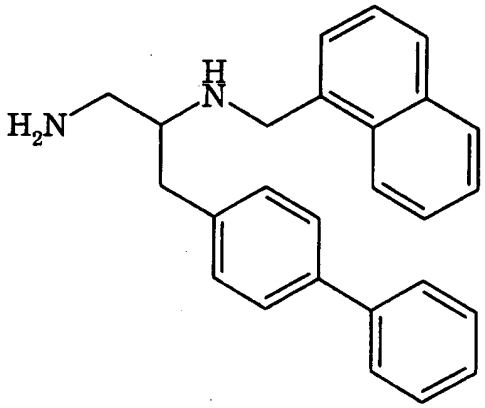
Preparation of 2-[(benzothien-3-yl)methylamino]-3-(naphth-1-yl)propylamine



MS 348

Example 85

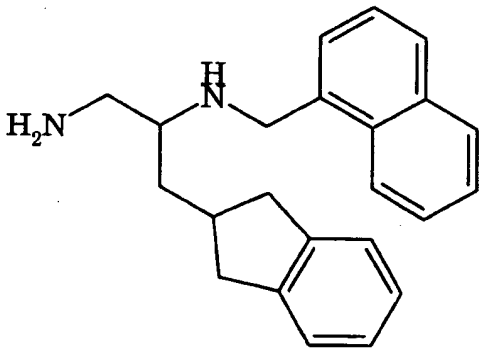
Preparation of 2-[4-(naphth-1-yl)benzylamino]-3-(4-biphenyl)propylamine



MS 367

Example 86

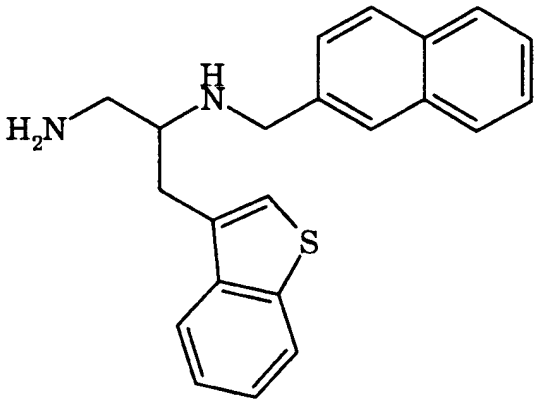
Preparation of 2-[(naphth-1-yl)methylamino]-3-(indan-2-yl)propylamine



MS 317

Example 87

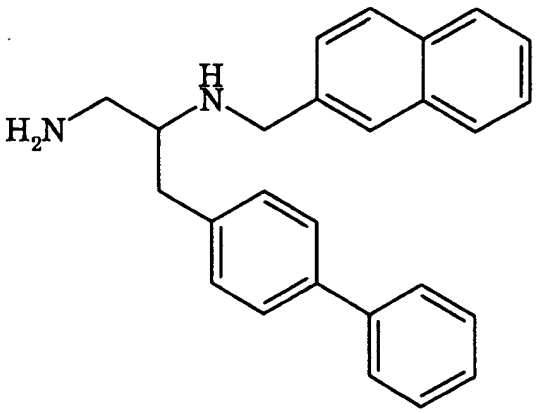
Preparation of 2-[(naphth-2-yl)methylamino]-3-(benzothien-3-yl)propylamine



MS 348

Example 88

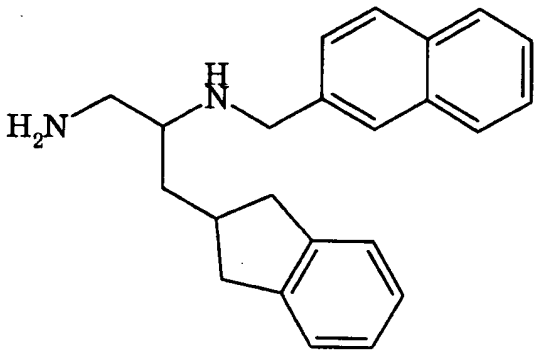
Preparation of 2-[(naphth-2-yl)methylamino]-3-(4-biphenyl)propylamine



MS 367

Example 89

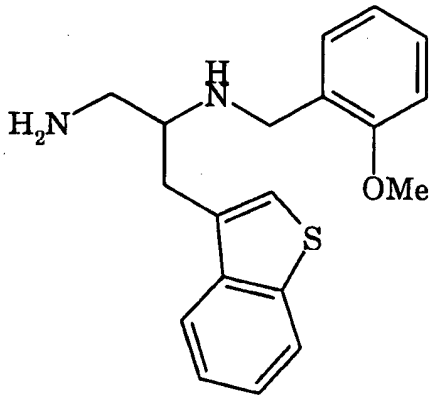
Preparation of 2-[(naphth-2-yl)methylamino]-3-(indan-2-yl)propylamine



MS 317

Example 90

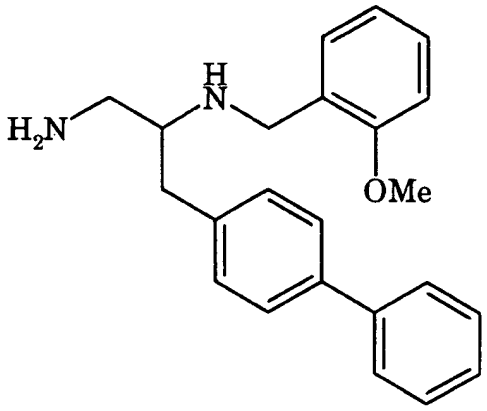
Preparation of 2-[(2-methoxyphenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 328

Example 91

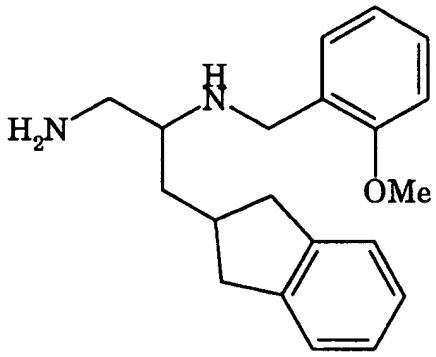
Preparation of 2-[2-methoxybenzylamino]-3-(4-biphenyl)propylamine



MS 347

Example 92

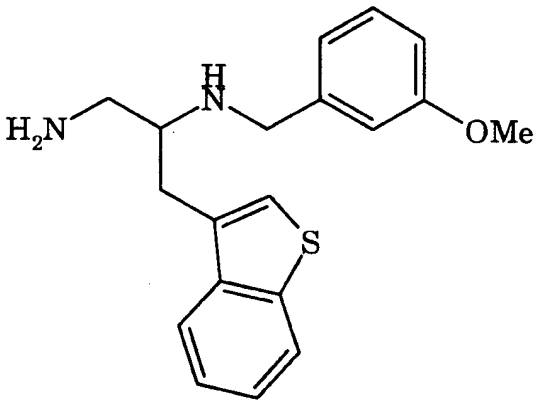
Preparation of 2-[(2-methoxyphenyl)methylamino]-3-(indan-2-yl)propylamine



MS 297

Example 93

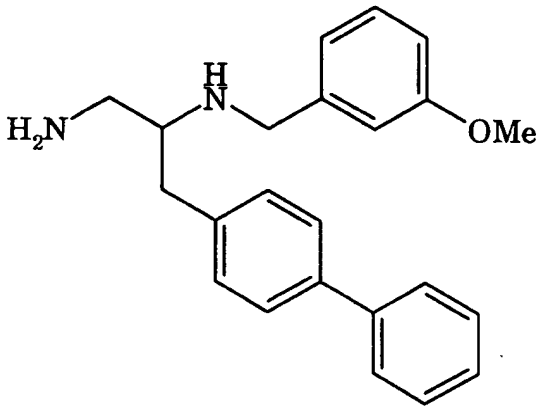
Preparation of 2-[(3-methoxyphenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 328

Example 94

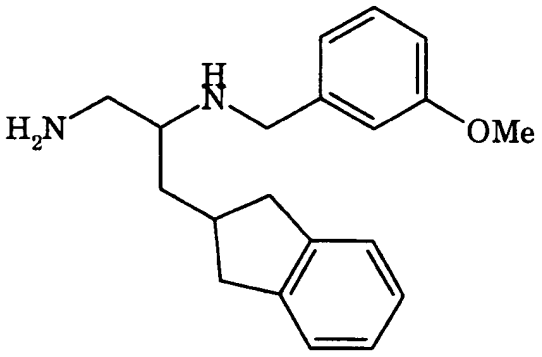
Preparation of 2-[3-methoxybenzylamino]-3-(4-biphenyl)propylamine



MS 347

Example 95

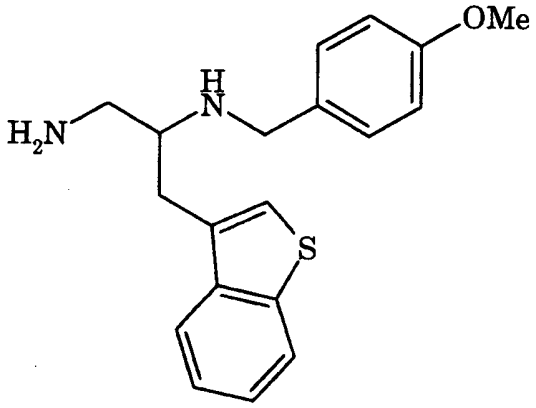
Preparation of 2-[(3-methoxyphenyl)methylamino]-3-(indan-2-yl)propylamine



MS 297

Example 96

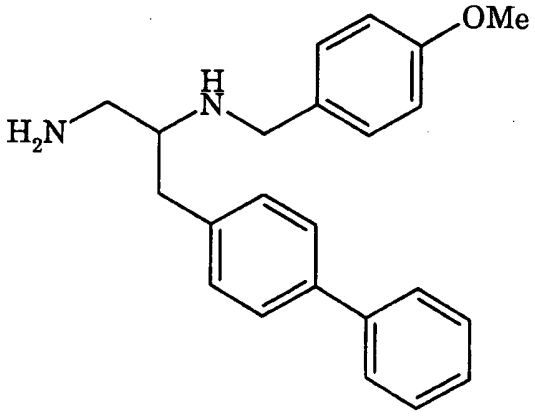
Preparation of 2-[(4-methoxyphenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 328

Example 97

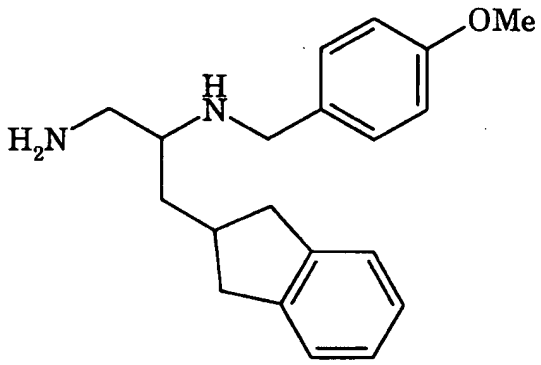
Preparation of 2-[4-methoxybenzylamino]-3-(4-biphenyl)propylamine



MS 347

Example 98

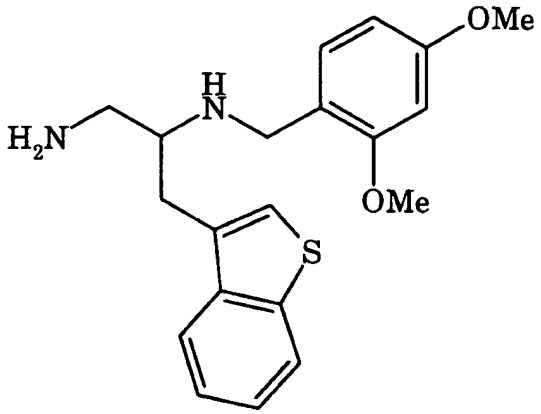
Preparation of 2-[(4-methoxyphenyl)methylamino]-3-(indan-2-yl)propylamine



MS 297

Example 99

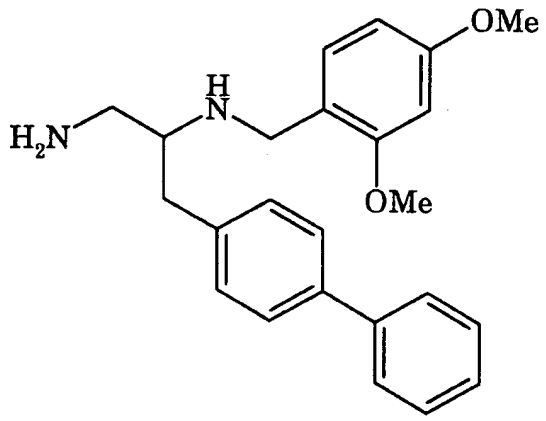
Preparation of 2-[(2,4-dimethoxyphenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS

Example 100

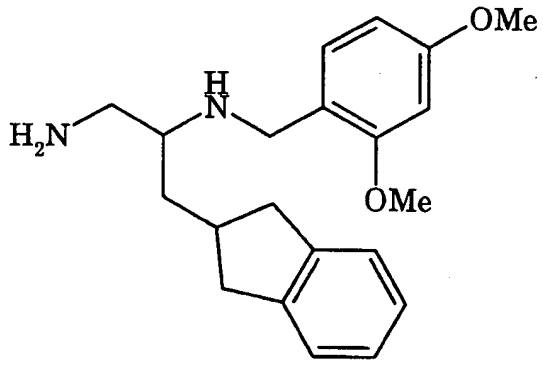
Preparation of 2-[2,4-dimethoxybenzylamino]-3-(4-biphenyl)propylamine



MS 377

Example 101

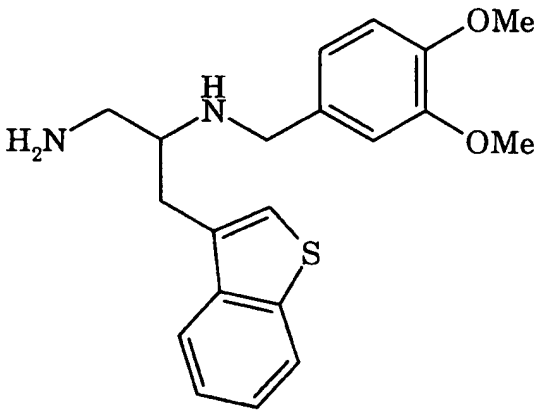
Preparation of 2-[(2,4-dimethoxyphenyl)methylamino]-3-(indan-2-yl)propylamine



MS

Example 102

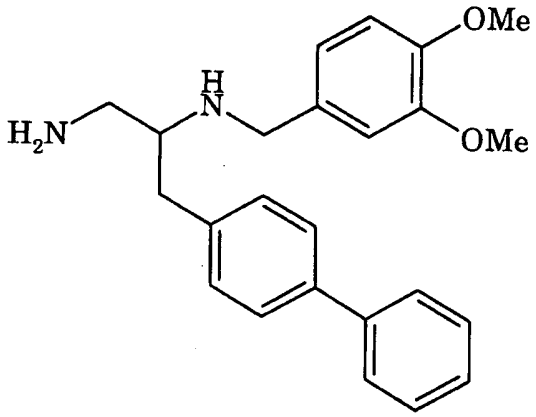
Preparation of 2-[(3,4-dimethoxyphenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 358

Example 103

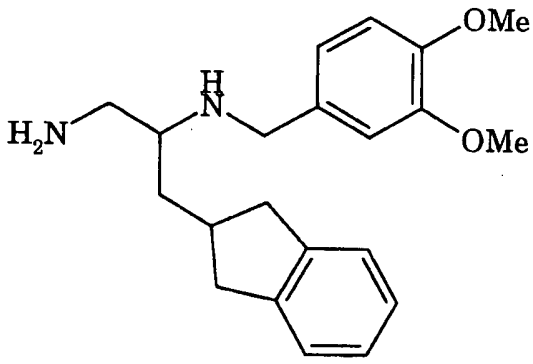
Preparation of 2-[3,4-dimethoxybenzylamino]-3-(4-biphenyl)propylamine



MS 377

Example 104

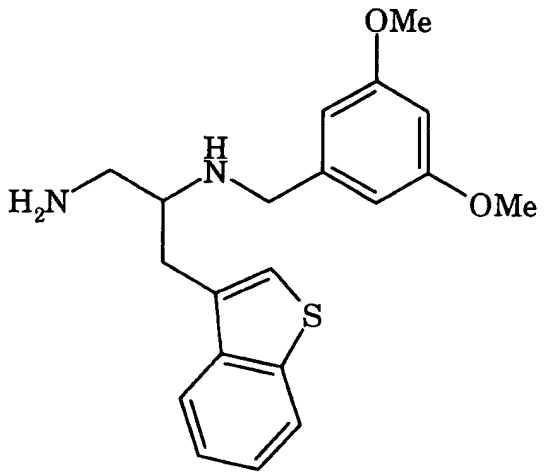
Preparation of 2-[(3,4-dimethoxyphenyl)methylamino]-3-(indan-2-yl)propylamine



MS 327

Example 105

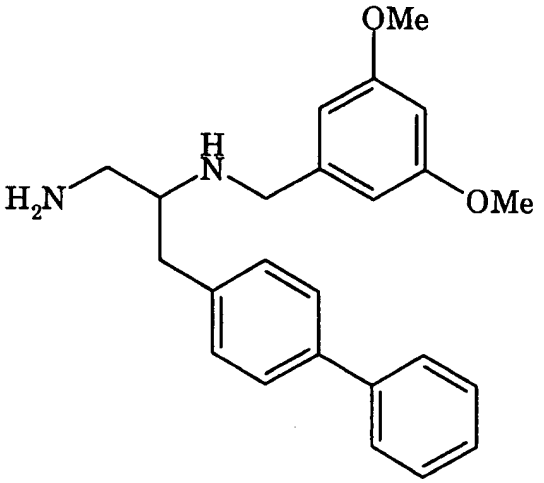
Preparation of 2-[(3,5-dimethoxyphenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 357

Example 106

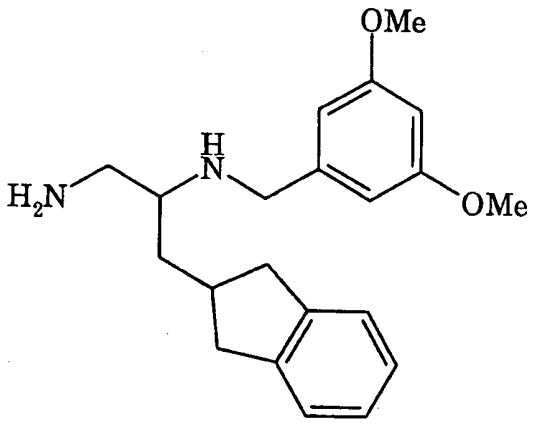
Preparation of 2-[3,5-dimethoxybenzylamino]-3-(4-biphenyl)propylamine



MS 377

Example 107

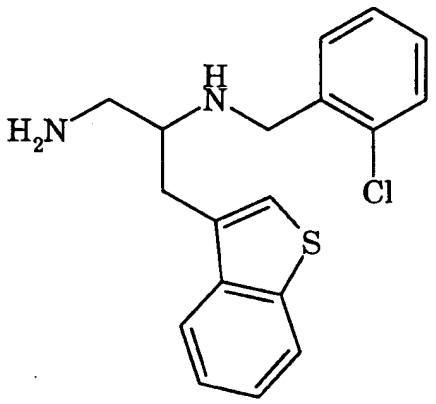
Preparation of 2-[(3,5-dimethoxyphenyl)methylamino]-3-(indan-2-yl)propylamine



MS

Example 108

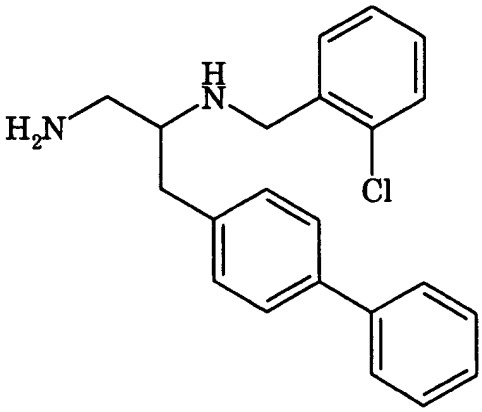
Preparation of 2-[(2-chlorophenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 331

Example 109

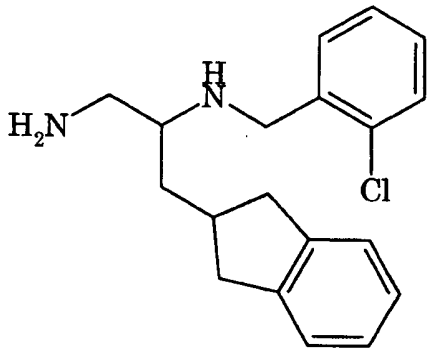
Preparation of 2-[2-chlorobenzylamino]-3-(4-biphenyl)propylamine



MS 351

Example 110

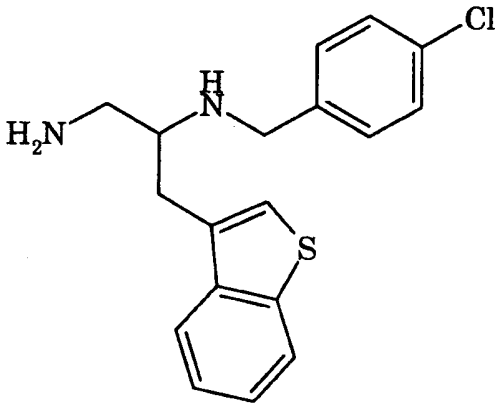
Preparation of 2-[(2-chlorophenyl)methylamino]-3-(indan-2-yl)propylamine



MS 301

Example 111

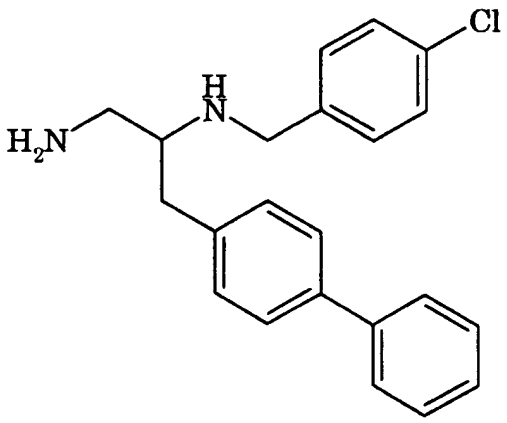
Preparation of 2-[(4-chlorophenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 331

Example 112

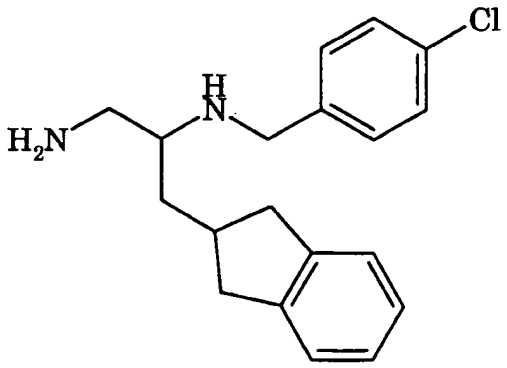
Preparation of 2-[4-chlorobenzylamino]-3-(4-biphenyl)propylamine



MS 351

Example 113

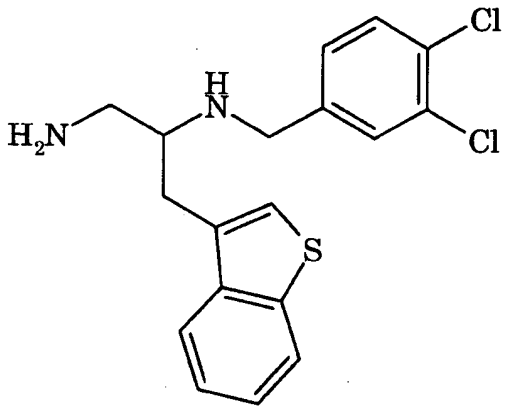
Preparation of 2-[(4-chlorophenyl)methylamino]-3-(indan-2-yl)propylamine



MS 301

Example 114

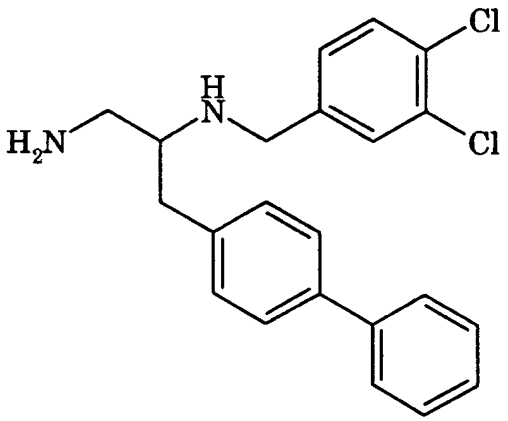
Preparation of 2-[(3,4-dichlorophenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 365

Example 115

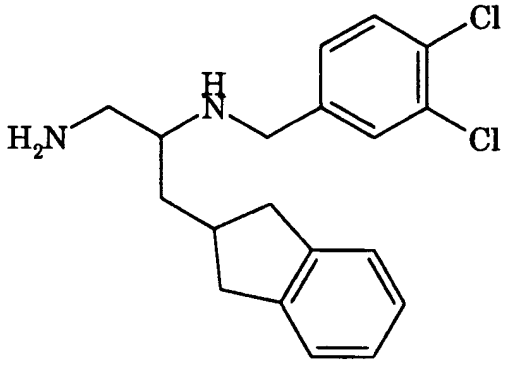
Preparation of 2-[3,4-dichlorobenzylamino]-3-(4-biphenyl)propylamine



MS 385

Example 116

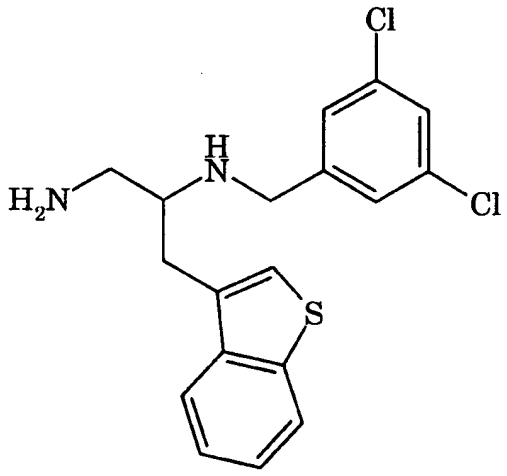
Preparation of 2-[(3,4-dichlorophenyl)methylamino]-3-(indan-2-yl)propylamine



MS 335

Example 117

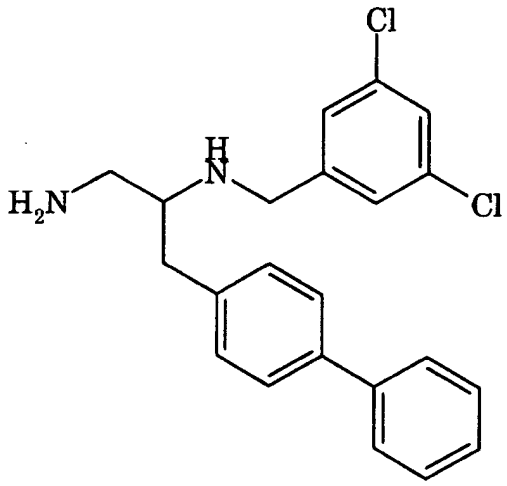
Preparation of 2-[(3,5-dichlorophenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 365

Example 118

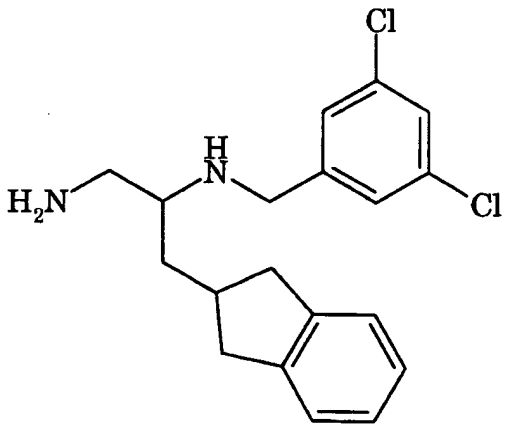
Preparation of 2-[3,5-dichlorobenzylamino]-3-(4-biphenyl)propylamine



MS 385

Example 119

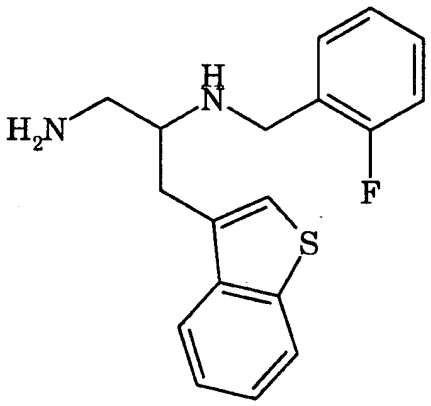
Preparation of 2-[(3,5-dichlorophenyl)methylamino]-3-(indan-2-yl)propylamine



MS 335

Example 120

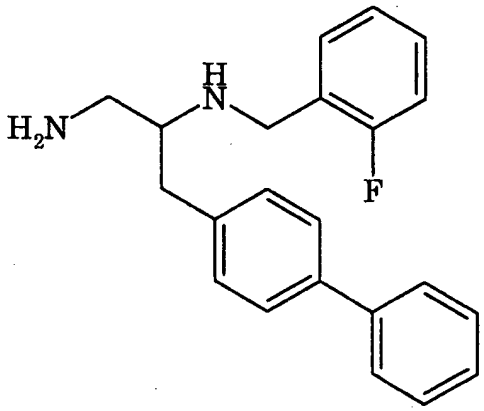
Preparation of 2-[(2-fluorophenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 314

Example 121

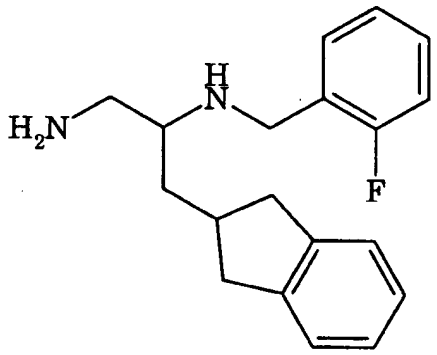
Preparation of 2-[2-fluorobenzylamino]-3-(4-biphenyl)propylamine



MS 335

Example 122

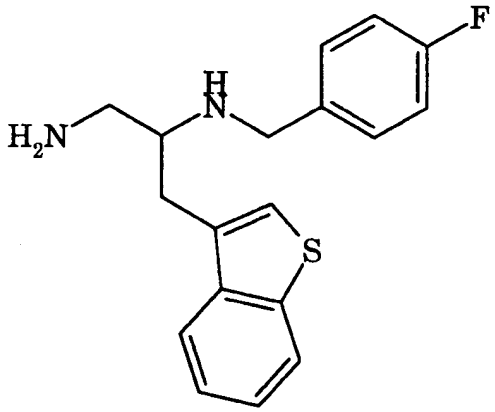
Preparation of 2-[(2-fluorophenyl)methylamino]-3-(indan-2-yl)propylamine



MS 285

Example 123

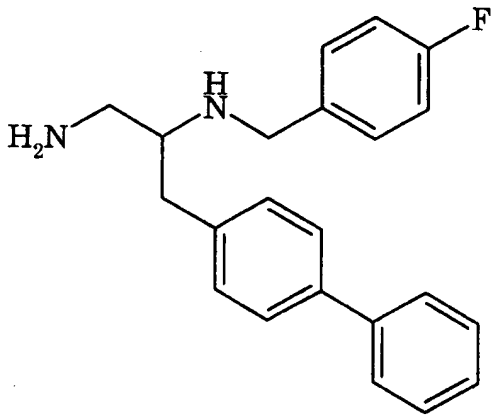
Preparation of 2-[(4-fluorophenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 314

Example 124

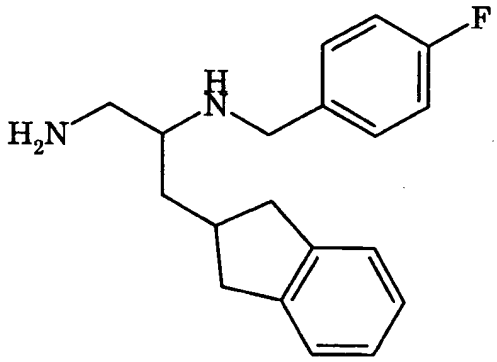
Preparation of 2-[4-fluorobenzylamino]-3-(4-biphenyl)propylamine



MS 335

Example 125

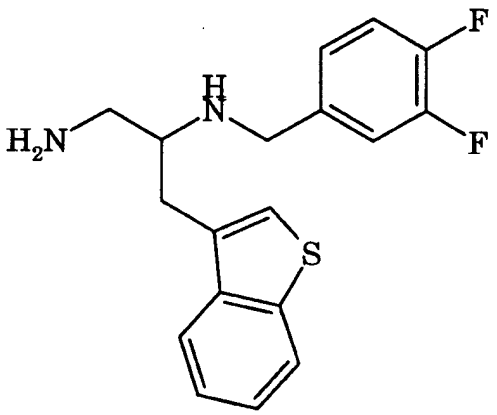
Preparation of 2-[(2-fluorophenyl)methylamino]-3-(indan-2-yl)propylamine



MS 285

Example 126

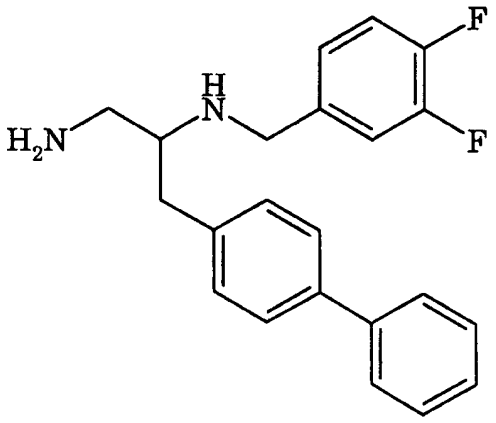
Preparation of 2-[(3,4-difluorophenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 332

Example 127

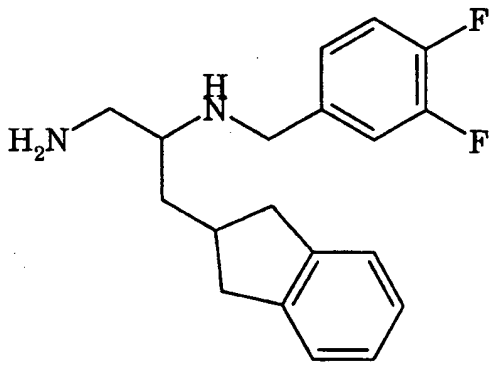
Preparation of 2-[3,4-difluorobenzylamino]-3-(4-biphenyl)propylamine



MS 353

Example 128

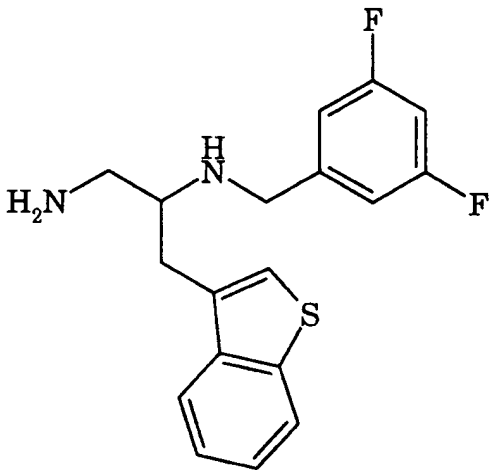
Preparation of 2-[(3,4-difluorophenyl)methylamino]-3-(indan-2-yl)propylamine



MS 303

Example 129

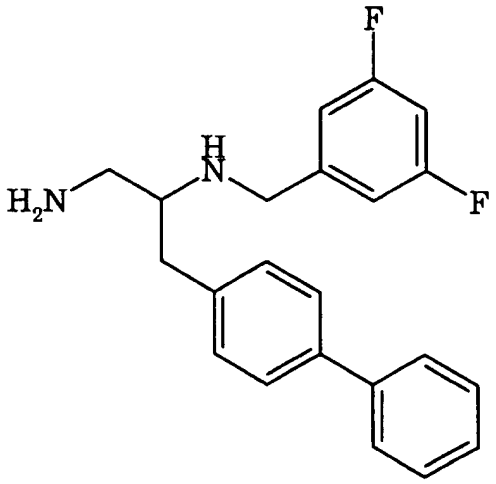
Preparation of 2-[(3,5-difluorophenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 332

Example 130

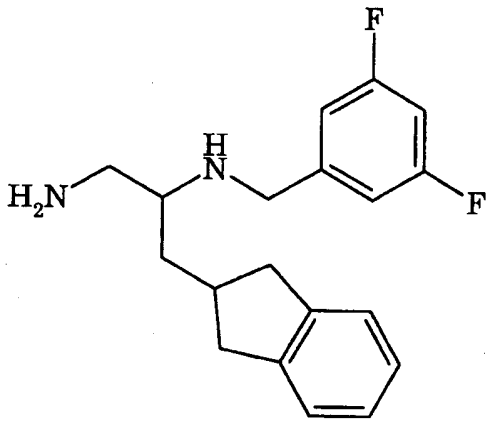
Preparation of 2-[3,5-difluorobenzylamino]-3-(4-biphenyl)propylamine



MS 353

Example 131

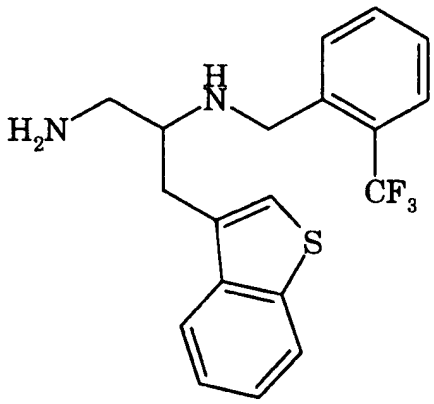
Preparation of 2-[(3,5-difluorophenyl)methylamino]-3-(indan-2-yl)propylamine



MS 303

Example 132

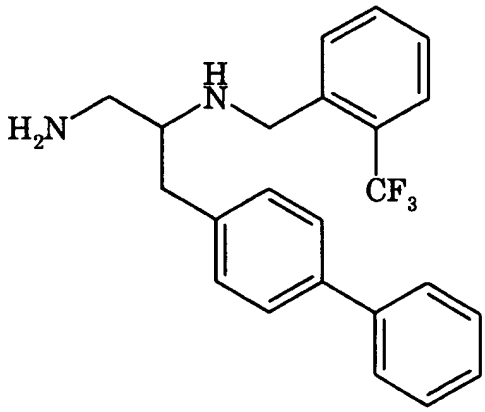
Preparation of 2-[(2-trifluoromethylphenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 364

Example 133

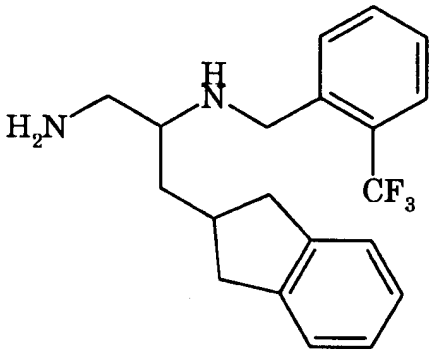
Preparation of 2-[2-trifluoromethylbenzylamino]-3-(4-biphenyl)propylamine



MS

Example 134

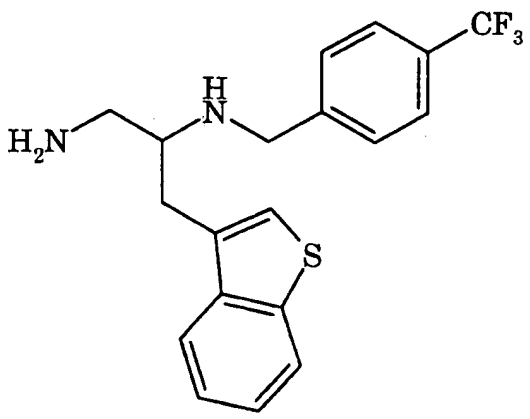
Preparation of 2-[(2-trifluoromethylphenyl)methylamino]-3-(indan-2-yl)propylamine



MS

Example 135

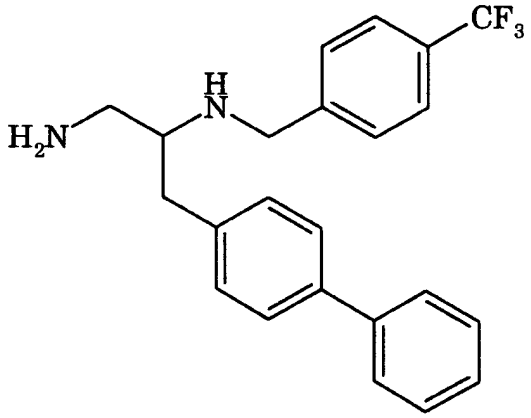
Preparation of 2-[(4-trifluoromethylphenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 364

Example 136

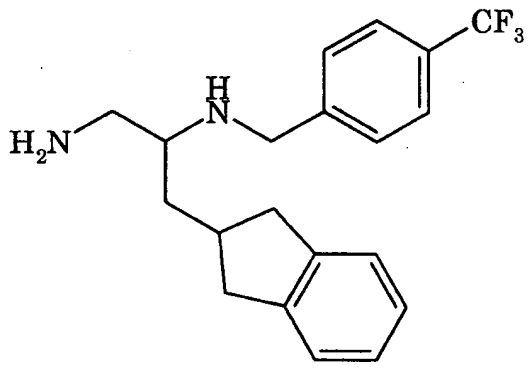
Preparation of 2-[4-trifluoromethylbenzylamino]-3-(4-biphenyl)propylamine



MS 385

Example 137

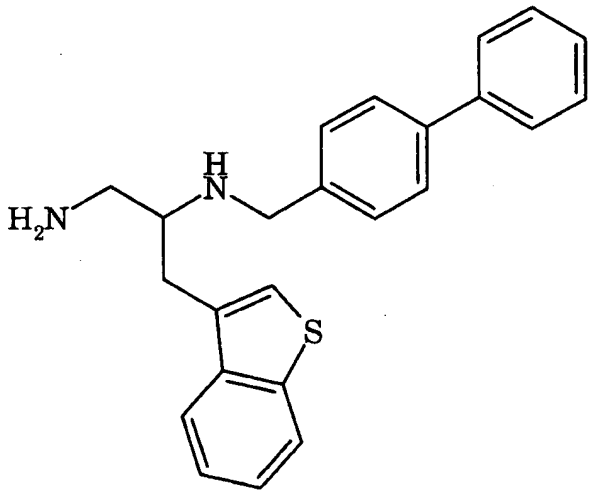
Preparation of 2-[(4-trifluoromethylphenyl)methylamino]-3-(indan-2-yl)propylamine



MS

Example 138

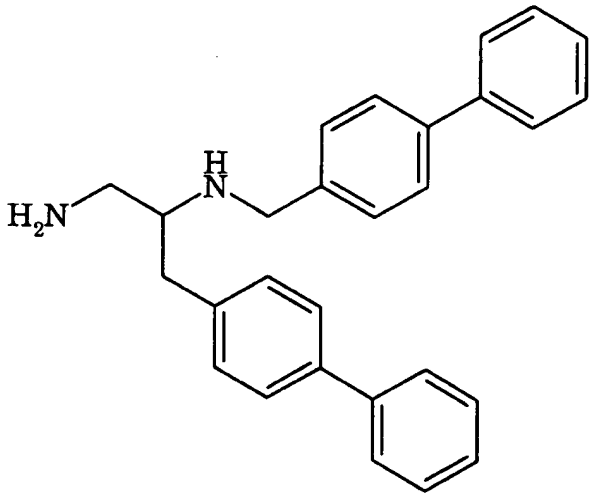
Preparation of 2-[(4-biphenyl)methylamino]-3-(benzothien-3-yl)propylamine



MS 373

Example 139

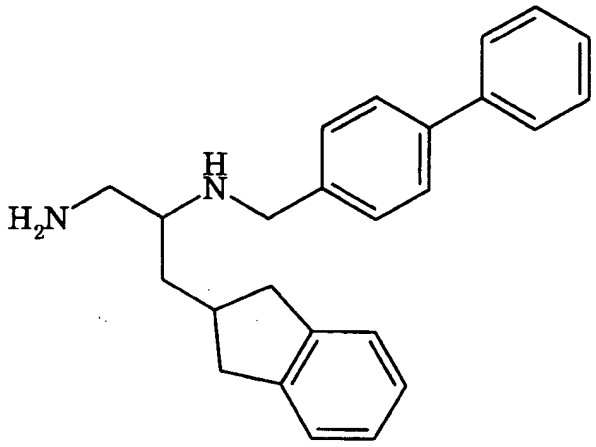
Preparation of 2-[(4-biphenyl)methylamino]-3-(4-biphenyl)propylamine



MS 393

Example 140

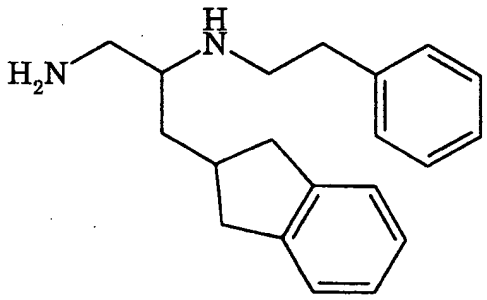
Preparation of 2-[(4-trifluoromethylphenyl)methylamino]-3-(indan-2-yl)propylamine



MS 343

Example 141

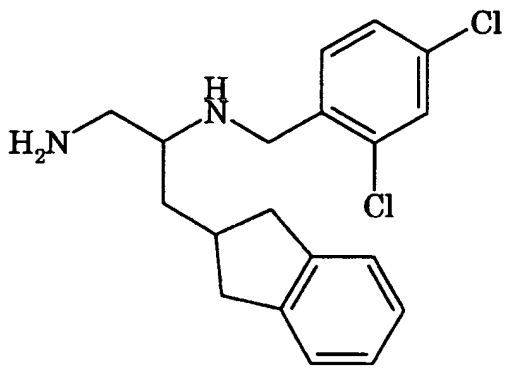
Preparation of 2-[2-(phenyl)ethylamino]-3-(indan-2-yl)propylamine



MS 281

Example 142

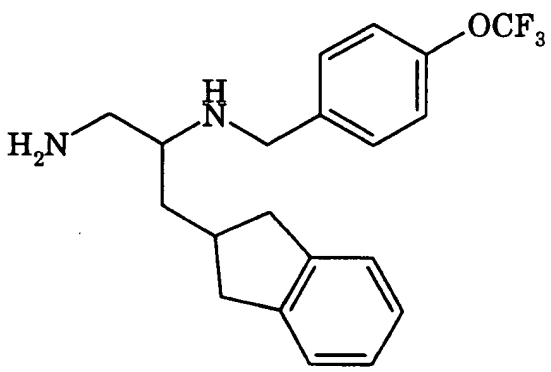
Preparation of 2-[(2,4-dichlorophenyl)methylamino]-3-(indan-2-yl)propylamine



MS 335

Example 143

Preparation of 2-[(4-trifluoromethoxyphenyl)methylamino]-3-(indan-2-yl)propylamine



MS 351

By substantially following the procedures described above one skilled in the art can prepare the other compounds of Formula I.

The compounds of the present invention bind to receptors specific for neuropeptide Y as well as the closely related neuropeptides. [For a

review of neuropeptide Y receptors, see, D. Gehlert, Life Sciences, 55:551-562 (1994)]. Receptors for neuropeptide Y and peptide YY have considerable overlap while pancreatic polypeptide appears to have its own distinct set of receptors. Many, but not all, of the effects of neuropeptide Y can be replicated using peptide YY.

Two subtypes of receptors for neuropeptide Y were initially proposed on the basis of the affinity of the 13-36 fragment of neuropeptide Y using a preparation of the sympathetic nervous system. While these are the best established receptors for neuropeptide Y, a substantial body of evidence exists that there are additional receptor subtypes. The best established is a Y-3 receptor that is responsive to neuropeptide Y, but not to peptide YY. Another recently delineated receptor has been described that binds peptide YY with high affinity and neuropeptide Y with lower affinity. While the pharmacology of the feeding response to neuropeptide Y appears to be Y-1 in nature, a separate "feeding receptor" has been proposed. The Y-1 receptor is the only one that has been successfully cloned to date. The following paragraphs summarize the available information on the known neuropeptide Y receptor subtypes and their potential role in physiological function.

Y-1 Receptor

The Y-1 receptor is the best characterized receptor for neuropeptide Y. This receptor is generally considered to be postsynaptic and mediates many of the known actions of neuropeptide Y in the periphery. Originally, this receptor was described as having poor affinity for C-terminal fragments of neuropeptide Y, such as the 13-36 fragment, but interacts with the full length neuropeptide Y and peptide YY with equal affinity. C. Wahlestedt, et al., Regulatory Peptides, 13:307-318 (1986); C. Wahlestedt, et al., NEURONAL MESSENGERS IN VASCULAR FUNCTION, 231-241 (Nobin, et al., eds. 1987). Substitution of the amino acid at position 34 with a proline (Pro^{34}) results in a protein which is specific for the Y-1 receptor. E.K. Potter, et al., European Journal of Pharmacology, 193:15-19 (1991). This tool has been used to establish a role for the Y-1 receptor in a variety of functions. The receptor is thought to be coupled to adenylate cyclase in an inhibitory manner in cerebral cortex, vascular smooth muscle cells, and SK-N-MC. [For a review, see, B.J. McDermott, et al., Cardiovascular Research, 27:893-905 (1993)]. This action is prevented by application of pertussis toxin confirming

the role of a G-protein coupled receptor. The Y-1 receptor mediates the mobilization of intracellular calcium in a porcine vascular smooth muscle cells and human erythroleukemia cells.

The cloned human Y-1 receptor can couple to either phosphotidylinositol hydrolysis or the inhibition of adenylate cyclase, depending on the type of cell in which the receptor is expressed. H. Herzog, et al., Proceedings of the National Academy of Sciences (USA), 89:5794-5798 (1992). The Y-1 receptor has been reported to couple to either second messenger system when studied using tissue preparations or cell lines naturally expressing the receptor. D. Gehlert, supra, at 553. The Y-1 receptor cannot, therefore, be distinguished solely on the basis of coupling to a single second messenger.

Modulation of a Y-1 receptor (either a typical or an atypical Y-1 receptor) is believed to influence multiple physiological conditions, including, but not limited to , obesity or appetite disorder, adult onset diabetes, bulimia nervosa, pheochromocytoma-induced hypertension, subarachnoid hemorrhage, neurogenic vascular hypertrophy, hypertension, anxiety, and anorexia nervosa. PCT Patent Publication WO 96/16542, published June 6, 1996, at page 135, and the references cited therein.

Y-2 Receptor

As with the Y-1 receptor, this receptor subtype was first delineated using vascular preparations. Pharmacologically, the Y-2 receptor is distinguished from Y-1 by exhibiting affinity for C-terminal fragments of neuropeptide Y. The receptor is most often differentiated by the use of neuropeptide Y(13-36), though the 3-36 fragment of neuropeptide Y and peptide YY provides improved affinity and selectivity. Y. Dumont, et al., Society for Neuroscience Abstracts, 19:726 (1993). Like Y-1 receptor, this receptor is coupled to the inhibition of adenylate cyclase, though in some preparations it may not be sensitive to pertussis toxin. The Y-2 receptor was found to reduce the intracellular levels of calcium in the synapses by selective inhibition of N-type calcium channels. Like the Y-1 receptor, the Y-2 receptor may exhibit differential coupling to second messengers. The Y2 receptor is believed to be involved in modulating hypertension, epileptic seizure, and neurogenic vascular hypertrophy. PCT Patent Publication WO 96/16542, published June 6, 1996, at page 135, and the references cited therein.

The Y-2 receptors are found in a variety of brain regions, including the hippocampus, substantia nigra-lateralis, thalamus, hypothalamus, and brainstem. In the periphery, Y-2 is found in the peripheral nervous system, such as sympathetic, parasympathetic, and sensory neurons. In all these tissues, Y-2 receptors mediate a decrease in the release of neurotransmitters.

Y-3 Receptor

This receptor is the newest and least studied of the established neuropeptide Y receptor subtypes. While neuropeptide Y is a fully efficacious agonist at this receptor population, peptide YY is weakly efficacious. This pharmacological property is used to define this receptor. A receptor that has similar pharmacology to the Y-3 receptor has been identified in the CA3 region of the hippocampus using electrophysiological techniques. This receptor may potentiate the excitatory response of these neurons to N-methyl-D-aspartate (NMDA). F.P. Monnet, et al., European Journal of Pharmacology, 182:207-208 (1990). This receptor is believed to modulate hypertension. PCT Patent Publication WO 96/16542, published June 6, 1996, at page 135, and the references cited therein.

The presence of this receptor is best established in the rat brainstem, specifically in the nucleus tractus solitarius. Application of neuropeptide Y to this region produces a dose-dependent reduction in blood pressure and heart rate. This area of the brain also may have significant contributions from the Y-1 and Y-2 receptor. Neuropeptide Y also inhibits the acetylcholine-induced release of catecholamines from the adrenal medulla, presumably through a Y-3 receptor. C. Wahlestedt, et al., Life Sciences, 50:PL7-PL14 (1992).

Peptide YY Preferring Receptor

A fourth receptor has been described that exhibits a modest preference for peptide YY over neuropeptide Y. This receptor was first described in the rat small intestine as having a 5-10 fold higher affinity for peptide YY over neuropeptide Y. M. Laburthe, et al., Endocrinology, 118:1910-1917 (1986). Subsequently, this receptor was found in the adipocyte and a kidney proximal tubule cell line. This receptor is coupled in an inhibitory manner to adenylate cyclase and is sensitive to pertussis toxin.

In the intestine, this receptor produces a potent inhibition of fluid and electrolyte secretion. The receptor is localized to the crypt cells where intestinal chloride secretion is believed to take place. The peptide YY preferring receptor in adipocytes mediates a reduction in lipolysis by way of a cyclic adenosine monophosphate (cAMP)-dependent mechanism.

"Feeding Receptor"

One of the earliest discovered central effects of neuropeptide Y was a profound increase in food intake that was observed following the hypothalmic administration of the peptide to rats. The response was greatest when the peptide was infused into the perifornical region of the hypothalamus. B.G. Stanley, et al., Brain Research, 604:304-317 (1993). While the pharmacology of this response resembled the Y-1 receptor, the 2-36 fragment of neuropeptide Y was significantly more potent than neuropeptide Y. In addition, intracerebroventricular neuropeptide Y(2-36) fully stimulates feeding, but does not reduce body temperature as does full length neuropeptide Y. F.B. Jolicoeur, et al., Brain Research Bulletin, 26:309-311 (1991). Recent patent publications describe the cloning and expression of the Y5 receptor, believed to be the "feeding receptor". Patent Cooperation Treaty Publication WO 96/16542, published June 6, 1996; Australian Patent Publication AU 956467 A0, published November 30, 1995; and United States Patent 5,602,024, issued February 11, 1997, the entire contents of which are herein incorporated by reference.

The biological activity of the compounds of the present invention was evaluated employing an initial screening assay which rapidly and accurately measured the binding of the tested compound to known neuropeptide Y receptor sites. Assays useful for evaluating neuropeptide Y receptor antagonists are well known in the art. See, e.g., United States Patents 5,284,839, issued February 8, 1994, which is herein incorporated by reference. See also, M.W. Walker, et al., Journal of Neurosciences, 8:2438-2446 (1988).

Neuropeptide Y Binding Assay

The ability of the compounds of the instant invention were assessed as to their ability to bind to neuropeptide Y using a protocol essentially as described in M.W. Walker, et al., supra. In this assay the cell line SK-N-MC was employed. This cell line was received from Sloane-Kettering Memorial Hospital, New York. These cells were cultured in T-150 flasks using Dulbecco's Minimal Essential Media (DMEM) supplemented with 5% fetal calf serum. The cells were manually removed from the flasks by scraping, pelleted, and stored at -70°C.

The pellets were resuspended using a glass homogenizer in 25 mM HEPES (pH 7.4) buffer containing 2.5 mM calcium chloride, 1 mM magnesium chloride, and 2 g/L bacitracin. Incubations were performed in a final volume of 200 µl containing 0.1 nM ^{125}I-peptide YY (2200 Ci/mmol) and 0.2-0.4 mg protein for about two hours at room temperature.

Nonspecific binding was defined as the amount of radioactivity remaining bound to the tissue after incubating in the presence of 1 µM neuropeptide Y. In some experiments various concentrations of compounds were included in the incubation mixture.

Incubations were terminated by rapid filtration through glass fiber filters which had been presoaked in 0.3% polyethyleneimine using a 96-well harvester. The filters were washed with 5 ml of 50 mM Tris (pH 7.4) at 4°C and rapidly dried at 60°C. The filters were then treated with melt-on scintillation sheets and the radioactivity retained on the filters were counted. The results were analyzed using various software packages. Protein concentrations were measured using standard coumassie protein assay reagents using bovine serum albumin as standards.

Y5 Binding

The ability of the compounds of Formula I to bind to the Y5 receptor was demonstrated employing assays essentially similar to those in United States Patent 5,602,024, issued February 11, 1997. The major distinction between the assays described therein and those employed in the present invention is the specific sequence of the Y5 receptor employed. The

present invention employs a truncated form of the receptor described in the above-identified patent, said receptor initiating at an internal initiation codon. Such a receptor exhibits pharmacological characteristics more consistent with those observed in vivo.

Many of the compounds prepared supra showed significant activity as neuropeptide Y receptor antagonists. As the compounds of Formula I are effective neuropeptide Y receptor antagonists, these compounds are of value in the treatment of a wide variety of clinical conditions which are characterized by the presence of an excess of neuropeptide Y. Thus, the invention provides methods for the treatment or prevention of a physiological disorder associated with an excess of neuropeptide Y, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt, solvate or prodrug thereof. The term "physiological disorder associated with an excess of neuropeptide Y" encompasses those disorders associated with an inappropriate stimulation of neuropeptide Y receptors, regardless of the actual amount of neuropeptide Y present in the locale.

These physiological disorders include:

disorders or diseases pertaining to the heart, blood vessels or the renal system, such as vasospasm, heart failure, shock, cardiac hypertrophy, increased blood pressure, angina, myocardial infarction, sudden cardiac death, arrythmia, peripheral vascular disease, and abnormal renal conditions such as impaired flow of fluid, abnormal mass transport, or renal failure;

conditions related to increased sympathetic nerve activity for example, during or after coronary artery surgery, and operations and surgery in the gastrointestinal tract;

cerebral diseases and diseases related to the central nervous system, such as cerebral infarction, neurodegeneration, epilepsy, stroke, and conditions related to stroke, cerebral vasospasm and hemorrhage, depression, anxiety, schizophrenia, cocaine addiction, and dementia;

conditions related to pain or nociception;

diseases related to abnormal gastrointestinal motility and secretion, such as different forms of ileus, diarrhea, gastric ulcer, neurogenic voiding dysfunction, urinary incontinence, and Crohn's disease;

abnormal drink and food intake disorders, such as obesity, anorexia, bulimia, and metabolic disorders;

diseases related to sexual dysfunction and reproductive disorders;

conditions or disorders associated with inflammation;

respiratory diseases, such as asthma and conditions related to asthma and bronchoconstriction; and

diseases related to abnormal hormone release, such as luteinizing hormone, growth hormone, insulin, and prolactin.

The compounds of Formula I are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

The present invention also includes methods employing pharmaceutical compositions which contain, as the active ingredient, the compounds of Formula I associated with pharmaceutically acceptable carriers. In making the compositions of the present invention the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally

adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compound is effective over a wide dosage range. For examples, dosages per day normally fall within the range of about 0.5 to about 30 mg/kg of body weight. In the treatment of adult humans, the range of about 1 to about 15 mg/kg/day, in single or divided dose, is especially preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several smaller doses for administration throughout the day.

For preparing solid compositions such as tablets the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder

compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The following examples illustrate the pharmaceutical compositions of the present invention.

Formulation Preparation 1

Hard gelatin capsules containing the following ingredients are prepared:

Ingredient	Quantity (mg/capsule)
Active Ingredient	30.0
Starch	305.0
Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Formulation Preparation 2

A tablet formula is prepared using the ingredients below:

Ingredient	Quantity (mg/tablet)
Active Ingredient	25.0
Cellulose, microcrystalline	200.0
Colloidal silicon dioxide	10.0
Stearic acid	5.0

The components are blended and compressed to form tablets, each weighing 240 mg.

Formulation Preparation 3

A dry powder inhaler formulation is prepared containing the following components:

Ingredient	Weight %
Active Ingredient	5
Lactose	95

The active mixture is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Formulation Preparation 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

Ingredient	Quantity (mg/tablet)
Active Ingredient	30.0 mg
Starch	45.0 mg
Microcrystalline cellulose	35.0 mg
Polyvinylpyrrolidone (as 10% solution in water)	4.0 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1.0 mg
Total	120 mg

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50-60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

Formulation Preparation 5

Capsules, each containing 40 mg of medicament are made as follows:

Ingredient	Quantity (mg/capsule)
Active Ingredient	40.0 mg
Starch	109.0 mg
Magnesium stearate	1.0 mg
Total	150.0 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Formulation Preparation 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

Ingredient	Amount
Active Ingredient	25 mg
Saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Formulation Preparation 7

Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

Ingredient	Amount
Active Ingredient	50.0 mg
Xanthan gum	4.0 mg
Sodium carboxymethyl cellulose (11%) Microcrystalline cellulose (89%)	50.0 mg
Sucrose	1.75 g
Sodium benzoate	10.0 mg
Flavor and Color	q.v.
Purified water to	5.0 ml

The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

Formulation Preparation 8

Capsules, each containing 15 mg of medicament, are made as follows:

Ingredient	Quantity (mg/capsule)
Active Ingredient	15.0 mg
Starch	407.0 mg
Magnesium stearate	3.0 mg
Total	425.0 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425 mg quantities.

Formulation Preparation 9

An intravenous formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	250.0 mg
Isotonic saline	1000 ml

Formulation Preparation 10

A topical formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	1-10 g
Emulsifying Wax	30 g
Liquid Paraffin	20 g
White Soft Paraffin	to 100 g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

Formulation Preparation 11

Sublingual or buccal tablets, each containing 10 mg of active ingredient, may be prepared as follows:

Ingredient	Quantity Per Tablet
Active Ingredient(s)	10.0 mg
Glycerol	210.5 mg
Water	143.0 mg
Sodium Citrate	4.5 mg
Polyvinyl Alcohol	26.5 mg
Polyvinylpyrrolidone	15.5 mg
Total	410.0 mg

The glycerol, water, sodium citrate, polyvinyl alcohol, and polyvinylpyrrolidone are admixed together by continuous stirring and maintaining the temperature at about 90°C. When the polymers have gone into solution, the solution is cooled to about 50-55°C and the medicament is slowly admixed. The homogenous mixture is poured into forms made of an inert material to produce a drug-containing diffusion matrix having a thickness of about 2-4 mm. This diffusion matrix is then cut to form individual tablets having the appropriate size.

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference. Such

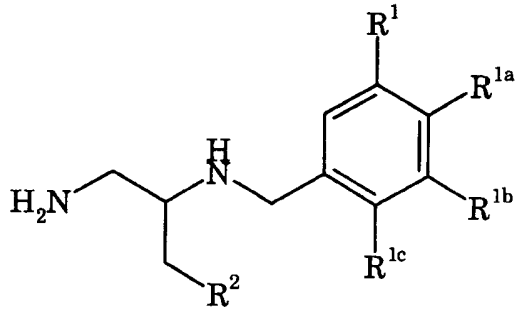
patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of biological factors to specific anatomical regions of the body, is described in U.S. Patent 5,011,472, issued April 30, 1991, which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs or prodrugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

We Claim:

1. A compound of the formula



wherein:

R^1, R^{1a}, R^{1b}, and R^{1c} are independently hydrogen, halo, C_1-C_6 alkoxy, C_1-C_6 alkyl, trifluoromethyl, trifluoromethoxy, or phenyl;

or R^1 and R^{1a}, together with the benzo ring to which they are attached, form a 2-naphthyl group;

or R^{1b} and R^{1c}, together with the benzo ring to which they are attached, form a 1-naphthyl group;

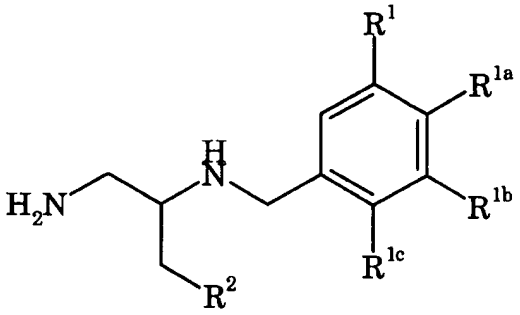
provided that no more than one of R^1, R^{1a}, R^{1b}, and R^{1c} is phenyl;

R^2 is naphthyl, pyridyl, phenyl, benzothienyl, indanyl, indenyl, indolyl, benzofuryl, or pyrrolyl,

said phenyl being optionally substituted with one or more moieties selected from the group consisting of halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, and trifluoromethyl;

or a pharmaceutically acceptable salt or solvate thereof.

2. A method of treating a condition associated with an excess of neuropeptide Y, or a related peptide, which comprises administering to a mammal in need thereof an effective amount of a compound of the formula



wherein:

R^1, R^{1a}, R^{1b}, and R^{1c} are independently hydrogen, halo, C_1-C_6 alkoxy, C_1-C_6 alkyl, trifluoromethyl, trifluoromethoxy, or phenyl;

or R^1 and R^{1a}, together with the benzo ring to which they are attached, form a 2-naphthyl group;

or R^{1b} and R^{1c}, together with the benzo ring to which they are attached, form a 1-naphthyl group;

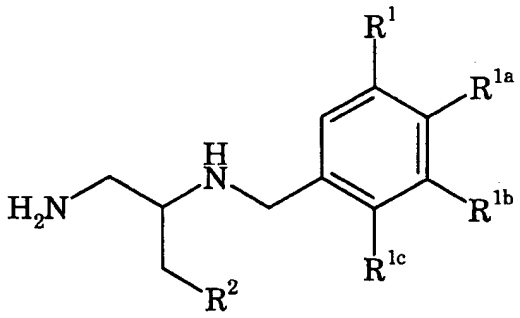
provided that no more than one of R^1, R^{1a}, R^{1b}, and R^{1c} is phenyl;

R^2 is naphthyl, pyridyl, phenyl, benzothienyl, indanyl, indenyl, indolyl, benzofuryl, or pyrrolyl,

said phenyl being optionally substituted with one or more moieties selected from the group consisting of halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, and trifluoromethyl;

or a pharmaceutically acceptable salt or solvate thereof.

3. A pharmaceutical formulation comprising a compound of the formula



wherein:

R^1, R^{1a}, R^{1b}, and R^{1c} are independently hydrogen, halo, C_1-C_6 alkoxy, C_1-C_6 alkyl, trifluoromethyl, trifluoromethoxy, or phenyl;

or R^1 and R^{1a}, together with the benzo ring to which they are attached, form a 2-naphthyl group;

or R^{1b} and R^{1c}, together with the benzo ring to which they are attached, form a 1-naphthyl group;

provided that no more than one of R^1, R^{1a}, R^{1b}, and R^{1c} is phenyl;

R^2 is naphthyl, pyridyl, phenyl, benzothienyl, indanyl, indenyl, indolyl, benzofuryl, or pyrrolyl,

said phenyl being optionally substituted with one or more moieties selected from the group consisting of halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, and trifluoromethyl;

or a pharmaceutically acceptable salt or solvate thereof, in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients therefor.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10264

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07C 211/00; A01N 33/02
US CL : 564/372; 514/649
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 564/372; 514/649

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REGISTRY, HCAPLUS, HCAOLD, USPATFULL structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,530,009 A (CHO et al.) 25 June 1996, see entire document.	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of citad documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 31 AUGUST 1998	Date of mailing of the international search report 08OCT1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Dwayne C. Jones DWAYNE C. JONES Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★